CHAPTER - I

Chemical Transformation of 10-DAB III in search of New Taxol Analogues
SEARCH FOR TAXOL ANALOGUES AS EFFICIENT ANTI-CANCER AGENTS.

Cancer is a dreaded disease whose existence was recognized thousands of years ago. The term 'cancer' was coined by Hippocrates in the 5th century B.C which means 'crab' in Latin. Cancer is characterised by unregulated proliferation of cells which arise from once normal body cells. There are several initiating factors, cofactors, promoters and various other agents involved in this transformation process. Although there are several types of cancer, most of them fall into three general categories.

1. Carcinomas : These arise from epithelial cells (e.g. lung, breast, colon, intestine, liver etc)

2. Sarcomas : These are of mesodermal origin (e.g. bone, muscle etc)

3. Lymphomas and leukemia : These originate from cells of blood and lymph glands.

In 1960, under Dr. J. H. Hartwell, National Cancer Institute (NCI) of USA embarked on one of the most ambitious drug research program of screening some 40,000 herbs for potential cancer curing chemicals. The pacific yew (Taxus brevifolia) was also included in the list as one of the plants to be screened. Using
bioactivity-guided fractionation, the active principle, named taxol, was isolated in 1967. Its structure \( \text{1} \) was elucidated in 1971 by Wani et al\(^1\) and cytotoxic activity studied.\(^2\) This antitumor agent taxol, originally developed by NCI of USA, is now marketed by Bristol Myers Squibb Co. Taxol is a novel highly functionalized diterpenoid comprising of a taxane nucleus with four ester groups attached to it. It is named as \( 5\beta,20\text{-epoxy-1,2\alpha,4,7\beta,10\beta,13\alpha\text{-hexahydroxytax-11-en-9-one-4,10-diacetate-2-benzoate-13-ester with (2'\text{R},3'S)\text{-N-benzoyl-3-phenylisoserine.}} } \)

The slow progress in the development of the antitumor drug taxol after the initial discovery of its cytotoxicity was caused by tedious isolation, extraction and purification procedure. \( \text{Taxus brevifolia} \), the tree from which taxol was initially isolated occurs in widely scattered areas and is slow growing (a tree needs 200 yrs. to reach its full size) and difficult to cultivate. Production of 1 Kg of taxol with current procedures requires about 25,000 pounds of dried bark of mature pacific yew trees. This translates to 750,000 trees to be sacrificed, assuming roughly 10 pounds of dried bark per tree.\(^3\) This accounts for the exorbitant cost of 2,00,000 to 3,00,000 US dollars per kilogram of taxol. Environmental considerations and the debatable abundance of the yew trees have
initiated the search for long-term alternative sources such as semisynthetic routes, cultivation and plant cell cultures.\textsuperscript{4}

It took more than two decades for taxol to reach the clinics after its discovery. In December 1992, the United States Food and Drug Administration approved of taxol for the treatment of drug refractory metastatic ovarian cancer and in April 1994 for the treatment of breast cancer. Taxotere (docetaxel)\textsuperscript{2} a semisynthetic taxol derivative was approved by FDA\textsuperscript{6} for the treatment of breast cancer in May 1996 and is currently undergoing phase II and III clinical trials for breast and lung cancer worldwide.\textsuperscript{7,8} Each year in the United states alone, the death toll of women suffering from ovarian cancer approaches approximately 12,000 out of 21,000 diagnosed with the disease.\textsuperscript{3} With established activity against metastatic ovarian cancer, including cisplatin refractory disease,\textsuperscript{9} breast cancer\textsuperscript{10,11} and promising results in the treatment of advanced lung cancer,\textsuperscript{12} squamous cell carcinoma of the head and neck,\textsuperscript{13} an estimated yearly demand for taxol in the United states alone could easily exceed 300Kg.

A major impediment in the development of taxol as a drug was its poor water solubility\textsuperscript{14} and the absence of salt forming functional groups. The low water solubility hampered in its formulation, caused undesirable side effects and multidrug resistance. The current technique is to solubilize taxol (6mg/ml) in a Cremophor EL (polyethoxylated castor oil/ethanol) mixture and to dilute this solution to the desired concentration with saline or 5% dextrose in water.\textsuperscript{15} Major drawback of the formulation is the hypersensitivity reactions caused by Cremophor EL which necessitates the use of prophylactic antiallergic
premedications such as dexamethasone, diphenylhydramine, cimetidine and longer periods of infusion. To overcome the problems associated with the low water solubility of taxol, the synthesis of taxol prodrugs has become an attractive area of research.

The present review gives an account of the recent developments towards structure modifications of taxol leading to newer taxol analogues and their structure-activity relationships.

**Mechanism of action:**

Taxol became anew the focus of interest in 1979 when Susan Horwitz and coworkers reported on the novel mechanism of action of the spindle poison. Instead of inducing microtubule disassembly like the vinca alkaloids (vincristine, vinblastine, colchicine), taxol promotes the polymerization of tubulin to microtubules and stabilizes them against depolymerization. Thus, the dynamic equilibrium of assembly and disassembly of microtubules is shifted in favor of the polymer, preventing cell division. Hence, taxol enhances both the rate and yield of microtubule assembly and lowers the critical concentration of tubulin required for microtubule formation.
Microtubules are an important component of the cytoskeleton of eukaryotic cells and play an essential role in cell division. These microtubules are not only fundamental components of spindle during the mitotic cycle, they are also intracellular transport vehicles and contribute to the cells shape and rigidity. Microtubules are spindle fibers that arise between the two sets of chromosomes in a dividing cell and pull the chromosome sets into position for forming two new cells, then they break down or dissolve away. Taxol kills the dividing cells by first helping the microtubules to form and then preventing its break down. Taxol binds preferentially to the β-tubulin subunit in a roughly equimolar ratio of one mole of taxol per one mole of polymerized tubulin dimer. If taxol is present, tubulin polymerizes without exogenous GTP or microtubule-associated proteins (MAPs). These stabilized and rigid microtubules cannot be disassembled by conditions normally used for depolymerization such as calcium ions or cold temperatures. Consequently, the dynamic organization of the cell is interrupted which leads to irreversible damage in rapidly dividing cells. There is also evidence that the antiproliferative activity of taxol is caused not only by tubulin polymerization but also by taxol's lipopolysaccharide (LPS) - like effects on macrophages.

Structure - Activity Relationships (SAR) :

Of particular interest to chemists are structure-activity relationship associated with the highly functionalized terpenoid skeletal system. The conformation of taxol is cup-shaped, with the northern hemisphere functionalities C-7 and C-10 oriented on the convex side while the southern hemisphere
functionalities at C-2, C-4 and the C-13 phenylisoserine side chain are located underneath on the concave side. In general, modification to the northern hemisphere of the molecule have little effect on biological activity, whereas modifications to the southern hemisphere have a marked impact. A vital feature for biological activity of taxol analogues is the ability to undergo hydrophobic collapse in aqueous media, thus positioning the C-4 acetate, the C-2 benzoyl and the C-3' phenyl groups in proximity to one another. Three levels of assays have been used in the structure-activity relationship studies: at the biochemical level, assays are used for either polymerization of tubulin or inhibition of depolymerization of microtubules; at the cellular level cytotoxicity is measured to tumor cell lines such as KB, J774, 2 macrophages, P388 leukemia or B16 melanoma and at the organism level, growth inhibition of either mouse tumors or human tumor xenografts are examined.

1. Modification of the diterpenoid moiety:

   a. C-6 modified analogs:

   Kingston and co-workers synthesized 6,7-epoxy paclitaxel 3, and analogs 4-8. None of the analogs were as effective as taxol in promoting the tubulin assembly. However, all the analogs except 4 and 7 stabilized the polymerized tubulin as well as or better than paclitaxel. Compounds 3, 4, 5 are comparable to paclitaxel in their cytotoxicity towards human Burkitt lymphoma CA 46 cells, while 6-8 were distinctly less cytotoxic. 6α-hydroxy paclitaxel 9, the principal metabolite of paclitaxel in human hepatic microsomes, human liver
slices and patient biliary excretions was also synthesized.\textsuperscript{23} Chen \textit{et al}\textsuperscript{26} reported that 6α-tosylate paclitaxel \textbf{10} to be 40-fold less potent than paclitaxel.

\begin{itemize}
  \item 4. \( R = H \)
  \item 5. \( R = \text{CH}_3\text{CO} \)
  \item 6. \( R = \text{PhCO} \)
  \item 7. \( R = \text{O-CH}_3\text{PhCO} \)
  \item 8. \( R = \text{Cyclo-C}_3\text{H}_2\text{CO} \)
  \item 9. \( R = H \)
  \item 10. \( R = \text{Ts} \)
\end{itemize}

\textbf{b. C-7 modified analogs :}

Hydroxyl group at position 7 of paclitaxel does not interact significantly with microtubule binding site. This was illustrated by the fact that acetylation at C-7 does not significantly alter the cytotoxicity while epimerization at C-7 only slightly reduces the in vitro activity.\textsuperscript{27} 7α-fluoro paclitaxel \textbf{11} showed excellent ability to polymerize tubulin in vitro and displayed potent cytotoxicity in HCT-116 cell lines.\textsuperscript{28,29} Johnson and collaborators\textsuperscript{30} studied the reaction of 2'-troc paclitaxel with methyl DAST which gave 2'-troc-7-deoxy-7α-fluoro taxol, 2'-troc-7-deoxy-7β,8β-methano taxol \textbf{12}. 
and 2'-troc-7-deoxy-Δ^{6,7}-taxol. Substitution of C-7 hydroxyl with azido group or a double bond at 6,7-position leads to 7α-azido-7-deoxy paclitaxel 13 and 7-deoxy-Δ^{6,7} paclitaxel 14 respectively, which are not as effective as taxol in promoting the tubulin binding but stabilized polymerized tubulin better than taxol.24

Two different groups reported that 7-deoxy paclitaxel is identical to paclitaxel in its cytotoxicity to the human colon carcinoma cell line HCT 116.31 Chen and co-workers have also observed that 7-epi-10-deoxy taxol 15 displayed potent activity.32 7-deoxy taxotere 16 and 7,10-dideoxy taxotere 17 showed a high level of cytotoxicity against P388 leukemia cell and excelled inhibition of disassembly of microtubules.33 Several more C-7 analogs such as 7-mesylate 18, 7-ethyl carbonate 19, 7-chloro methyl acetate, 7-epi-silyl ethers 20 were afforded.
from paclitaxel. 7-fluoro docetaxel 21 was three times more potent than paclitaxel, carbamate analogs 22 possessed marked reduced cytotoxicity whereas 7-epi-silyl ether analogs were inactive in both assays. Greenwald et al. synthesized several PEG conjugated paclitaxel derivatives 23 [MW>2000] which were highly water soluble while still maintaining a cytotoxicity profile. 7α-acetyl amino taxoid 24, paclitaxel-2',7-dinitrate ester 25, pyrazoline derivative of taxol 26 are some of the other analogs. This leads to the inference that modification at the C-7 position has minimal effect on the biological activities i.e. tubulin binding and cytotoxicity.

15. R1 = OH, R2 = H, R3 = Ph
16. R1 = H, R2 = OH, R3 = (Me)3CO
17. R1 = H, R2 = H, R3 = (Me)3CO
21. R1 = F, R2 = OH, R3 = (Me)3CO
24. R1 = NHCOCH3, R2 = OAc, R3 = Ph

18. R1 = H, R2 = Ms
19. R1 = H, R2 = CO2Et
20. R1 = H, R2 = TMS
22. R1 = H, R2 = CONHBu
23. R1 = H, R2 = COOR3 where R3 = CH3PEG 2000
25. R1 = R2 = NO2

26. a. R1 = Ph, R2 = Boc
    b. R1 = Ph, R2 = Bz
    c. R1 = isobutyl, R2 = Boc
c. C-9 modified analogs :

The sterically hindered C-9 carbonyl group of both taxol and baccatin III had earlier defied modifications. For example, it was reported Wahl et al that the carbonyl group could not be reduced with sodium borohydride or lithium aluminum hydride. However, the removal of the C-9 carbonyl function from the taxane skeleton resulted in an equally active 9-deoxo taxol. Simultaneous removal of the oxygenated function at C-7 and C-9 afforded 7-deoxy-9-deoxo taxol which suffered a little loss of activity, while 10-desacetoxy-7-deoxy-9-deoxo taxol was ten fold less active than taxol. 9(R)-dihydro taxol showed slightly greater antitumor activity than taxol and was found to be as active as taxol in the promotion microtubule assembly. Recently, Georg et al reported some reductions of the C-9 keto functionality. Electrochemical reduction of docetaxel yielded 9α-dihydro docetaxel and 9β-dihydro docetaxel. These docetaxel analogs retained a high level of in vitro cytotoxicity against P388 leukemia cells and are also excellent inhibitors of the disassembly of microtubules. 9α-dihydro baccatin-III was also achieved by Py and collaborators on reduction with diborane. Datta and co-workers reported the synthesis of 9-keto modified cyclic carbonates.

Analogs exhibited poor cytotoxic activity against B16 melanoma cells whereas they retained the microtubule assembling properties. Samarium diiodide reduction of paclitaxel, 10-DAB-III and docetaxel furnished
10-deacetoxy-9β-hydroxy paclitaxel 35, 10-deacetyl-9β-hydroxy baccatin III 36, 10-dehydroxy-9β-hydroxy docetaxel 37 and 9β-hydroxy docetaxel 37a respectively. The docetaxel analogs displayed activity in both cytotoxicity and microtubule assembly assay comparable to taxol. 9α,10α-dihydroxy paclitaxel 38 obtained on NaBH₄ reduction was resistant to further C-9 acetylation and oxidation. The compound exhibited microtubule assembly properties.
comparable to paclitaxel, however it was 3-4 times less cytotoxic against B16 melanoma cells.

d. C-10 modified analogs:

The 10-acetoxy group makes only a small contribution to the activity of taxol, while 10-deoxy series accentuates the activity of taxotere. 10-deacetoxy taxol 39 and 10-deoxy taxotere 40 were synthesized by using tributyltin hydride and AIBN. The former is comparable to taxol in its cytotoxicity in the P 388 cell culture system, while the latter is significantly more active than taxol.48 This confirms the fact that the C-10 acetoxy group is not involved in interaction at the binding site. This observation was reinforced by studies carried out by several groups49-52 on the synthesis of 10-deacetoxy taxol. Chen et al53 carried out an efficient synthesis of 7,10-dideoxy taxol 41 and 10-deoxy-7-epi taxol 42 with excellent yields. Compound 42 displayed potent biological activity comparable to taxol. Simple C-10 carbamate derivatives have also been prepared by reacting C-10-troc derivative of paclitaxel with primary amines.54 Kant and co-workers55 carried out modifications at C-10 position of paclitaxel and docetaxel to generate
ester, ether, carbonate and carbamate derivatives. Analogs 43-46 of C-10 modified taxotere displayed cytotoxic properties. The C-10 methyl ether 44 and methyl carbonate 45 are more cytotoxic than taxol or 10-acetoxy taxotere. They also exhibit better tubulin binding properties. C-10 modified paclitaxel analogues 47-52 showed tubulin binding properties similar to taxol but were less cytotoxic than the parent compound, except the C-10 carbamate 49.

Py and co-workers reported that 10-DAB III on reduction with SmI$_2$ furnished several products 7-epi-10-deacetyl baccatin III 53, 10-deacetoxy baccatin III 54, 7-epi-10-deacetoxy baccatin III 55 and 9β-dihyro-10-deacetoxy
baccatin III 56 depending on the solvent used. Thus the reactivity of the hydroxyl groups of 10-DAB-III towards acylating agents is of the order C(7)>C(10)>>C(13). A study of several C-10 monoesters revealed that 10-[(4-methoxy phenyl)acetyl], 10-(2-nitro benzoyl) and 10-(phenyl acetyl) esters were more active than paclitaxel. Selective acylation at C-10 was carried out with triflic anhydride in dimethylformamide and lanthanide trifluoromethane sulfonate.

e. C 11-12 modified analog:

Swindell et al reported that the presence of Δ11 double bond has little influence on the strain energy of the taxane system. But it is clear that the double bond contributes to the A-ring conformation and consequently to the side chain orientation. The bridge head double bond of baccatin III derivatives is totally unreactive towards catalytic hydrogenation. Infact the benzyl group at C-2 can be hydrogenated to the corresponding cyclohexane carboxylate without affecting the double bond of the terpenoid core. Marder and co-workers studied the reduction of the C-11/C-12 double bond of 13-oxo-10-deacetyl baccatin III using zinc in acidic or basic conditions leading to the 11,12-dihydro-10-deacetyl baccatin III 57 which was less active than 10-DAB-III in the microtubule disassembly assay. Because of its extremely folded structure 57 was resistant to esterification at C-13. A similar reduction also achieved with sodium borohydrate. Kelly and collaborators observed that the isotaxol analog 58 has the same potency as taxotere and 10-acetyltaxotere, whereas the potency of the 11,12-dihydro-12β-hydroxy taxotere analog 59 is reduced. Analog 60a 11,12-
To investigate the effect of the C-18 position of docetaxel in the cytotoxic activity, C-18 modified analogs were synthesized for the first time by Uoto and co-workers. The cytotoxic activity of analogs 61-66 was evaluated against four cell lines (PC-6, PC-6/v CR, PC-12, P 388). The acetoxy 61, acetamido 64 and morpholine 65 analogs which had polar substituents at the C-18 position, showed remarkably decreased activity. The formyl 66, azido 63 analogs showed a decrease in cytotoxic activity. This leads to the inference that dihydro-4-deacetyl docetaxel and its C-7 epimer 60b were found to be inactive in the microtubule assembly assay. Harriman et al. studied the epoxidation of the C-11/12 double bond.

f. C-18 modified analogs:

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the C-18 position has no steric allowance for the expression of the cytotoxic activity.

The importance of the C-2 benzoate group for bioactivity was demonstrated by the fact that 2-des(benzoyloxy) paclitaxel 67 shows modest in vitro cytotoxicity in human colon cancer cell line. Its in vivo ability to polymerize tubulin was also below measurable level. Studies by the Kingston group on hydrolysis with 7-(triethylsilyl)-hexahydro baccatin III have shown that the C-10 acetyl group is hydrolyzed first followed by the C-4 acetyl group and then the C-2 benzoyl group. This surprising hydrolysis of the tertiary ester preferentially in presence of the secondary ester at C-2 can be explained via an intramolecular assistance from the C-13 hydroxyl group. Similar results were also reported by the Potier group. The C-2 benzoate group could be selectively hydrolyzed with tert. BuOK while retaining the esters at C-10 and C-4. Reaction with anhydrous KOH resulted in the 2-debenzoyl derivatives 68 and 69. Analog 70 prepared by reaction with 4-chloro benzoic acid was found to be slightly more active than paclitaxel in the microtubule assembly assay but was three times less cytotoxic against B16 melanoma cells. Kingston et al observed the C-18 position has no steric allowance for the expression of the cytotoxic activity.

![Chemical structures and formulas](image-url)
two new class of 2-acyl paclitaxel analogs after initial hydrolysis of 2',7-bis(TES) paclitaxel under phase transfer catalysis. In P388 murine leukemia cell line, the para derivatives 72a, b, d were much less cytotoxic than paclitaxel, while the meta derivatives 71a, b, c, d were all significantly more active than taxol with cytotoxicities 150, 5, 800 and 700 times of taxol. Analog 71a was also found to promote tubulin assembly under conditions where taxol is inactive. Red Al was used to selectively remove the C-2 benzoate 7,13-bis TES baccatin and the resulting hydroxyl group was further converted to analogs 73-77. All these five analogs were inactive in both the tubulin polymerization as well as cytotoxicity assays. Ojima et al synthesized C-2 modified analog 2-hexahydro-docetaxel 78, through hydrogenolysis over 5% Rh on carbon, which showed similar tubulin binding ability as docetaxel. However, cytotoxicity of 78 was found to be 12-fold weaker than docetaxel against P388 cell line. These results clearly indicates that the presence of a phenyl or an aromatic ring at C-2 is not a requisite for strong binding to the tubulin receptor. Similar results were also obtained by Georg et al Nicolaou and coworkers synthesized 2-paclitaxel analogs by acylation of organolithium species by an intermediate 1,2-cyclic carbonate as the key reaction. Electrochemical reduction of 7,10,13-protected paclitaxel analog in a mixture of methanol and acetonitrile along with tetraethyl ammonium acetate and acetate buffer furnished C-2 modified analogs 79-84. Biological evaluation of these compounds revealed cytotoxicities comparable to docetaxel against P388 leukemia cell lines. 2-epi-paclitaxel 85 synthesized through the key intermediate 2-debenzoyl paclitaxel was found to be inactive in tubulin assembly assay and HCT 116 cytotoxicity assay. Georg et al synthesized 2-benzoate analogues 86-97 which did not exhibit any remarkable enhancement in biological activity in
the microtubule assembly assay at 37°C. Most of the analogues were found to possess biological properties similar to paclitaxel. 2-0-heteroaroyl substitution was found to be detrimental to cytotoxicity. Analogs 98-105 on evaluation of biological activity gave varied results.

The thienyl derivatives 101 and 102 elicited microtubule assembly properties comparable to paclitaxel, while the pyridyl (98-100), furyl (103, 104) and N-methyl pyrrole substituted taxanes all displayed diminished microtubule assembly properties compared to paclitaxel. But all the derivatives were found to be less cytotoxic than paclitaxel against B16 melanoma cell lines. These results lead to the conclusion that except for a few cases modification of the C-2 benzoate moiety completely destroys the antitumor activity.
73. \( R = \text{OAc}, R_1 R_2 = -C(O)H, R_3 = \text{Ph} \)
74. \( R = \text{OAc}, R_1 = \text{CONHCH}_2\text{H}_4\cdot\text{NO}_2-p, R_2 = \text{H}, R_3 = \text{Ph} \)
75. \( R = \text{OAc}, R_1 = \text{Bz-OMe-p}, R_2 = \text{H}, R_3 = \text{Ph} \)
76. \( R = \text{OAc}, R_1 = \text{Bz-NO}_2-p, R_2 = \text{H}, R_3 = \text{Ph} \)
77. \( R = \text{OAc}, R_1 = \text{COCH}_3H_4\cdot\text{N}-c, R_2 = \text{H}, R_3 = \text{Ph} \)
78. \( R = \text{OH}, R_1 = \text{COCH}_3H_4\cdot\text{Hf}, R_2 = \text{H}, R_3 = \text{OBu}^\text{t} \)
79. \( R_1 = \text{m-F-Ph}, R_2 = \text{H}, R_3 = \text{Bu}^\text{t} \)
80. \( R_1 = \text{m-Cl-Ph}, R_2 = \text{H}, R_3 = \text{Bu}^\text{t} \)
81. \( R_1 = \text{m-CF}_3\cdot\text{Ph}, R_2 = \text{H}, R_3 = \text{Bu}^\text{t} \)
82. \( R_1 = \text{p-F-Ph}, R_2 = \text{H}, R_3 = \text{Bu}^\text{t} \)
83. \( R_1 = \text{p-MeO-Ph}, R_2 = \text{H}, R_3 = \text{Bu}^\text{t} \)
84. \( R_1 = \text{p-CF}_3\cdot\text{Ph}, R_2 = \text{H}, R_3 = \text{Bu}^\text{t} \)
85. \( R_1 = \text{m-F-Ph}, R_2 = \text{H}, R_3 = \text{Bu}^\text{t} \)
86. \( \text{Ar} = \text{4-Cl phenyl} \)
87. \( \text{Ar} = \text{4-methoxy phenyl} \)
88. \( \text{Ar} = \text{4-methyl phenyl} \)
89. \( \text{Ar} = \text{3,4-dichloro phenyl} \)
90. \( \text{Ar} = \text{3-chloro phenyl} \)
91. \( \text{Ar} = \text{3-methyl phenyl} \)
92. \( \text{Ar} = \text{2-methyl phenyl} \)
93. \( \text{Ar} = \text{4-nitro phenyl} \)
94. \( \text{Ar} = \text{4-fluoro phenyl} \)
95. \( \text{Ar} = \text{3-trifluoromethyl phenyl} \)
96. \( \text{Ar} = \text{3,5-dichloro phenyl} \)
97. \( \text{Ar} = \text{3-nitrophenyl} \)
98. \( \text{Ar} = \text{2-pyridyl} \)
99. \( \text{Ar} = \text{3-pyridyl} \)
100. \( \text{Ar} = \text{4-pyridyl} \)
101. \( \text{Ar} = \text{2-thienyl} \)
102. \( \text{Ar} = \text{3-thienyl} \)
103. \( \text{Ar} = \text{2-furyl} \)
104. \( \text{Ar} = \text{3-furyl} \)
105. \( \text{Ar} = \text{2-N-methyl pyrrole} \)

h. C-1 modified analog:

2',7-bis (TES) paclitaxel on treatment with NaH and CS\textsubscript{2} in THF at room temperature furnished C-1 acyl migrated compound which on deoxygenation with Bu\textsubscript{3}SnH/AIBN yielded 1-benzoyl-2-des(benzoyloxy) paclitaxel 106. This compound was found to be less active than paclitaxel against P388 leukemia cell lines.\textsuperscript{79} This data therefore confirms that the presence of the
C-2 benzoate group is essential for the bioactivity of paclitaxel. Similar reaction was also reported by Chen et al.\textsuperscript{80}

i. C-4 modified analog:

Synthesis of 4-deacetyl paclitaxel 107 was reported by Kingston\textsuperscript{81,82} Georg\textsuperscript{83} and Gueritte-Voegelein.\textsuperscript{84} This compound was found to be less potent than paclitaxel in several in vitro assays. Chen et al.\textsuperscript{85} synthesized C-4 modified analogs 108 and 109 which were evaluated in an in vitro cytotoxicity assay against a human lung carcinoma cell line (HCT-116). The C-4 cyclopropyl paclitaxel analog 108 was more potent than paclitaxel while the C-4 benzoate analog 109 possessed only much reduced cytotoxicity. Kingston et al.\textsuperscript{86} reported the synthesis of 4-deacetoxy paclitaxel 110 and 4-deacetoxy-10-deacetyl paclitaxel 111. The cytotoxicity of compounds 110 and 111 was less than paclitaxel against human CA 46 Burkitt lymphoma cells. They were also less active than paclitaxel in promoting tubulin polymerization. The reduced activity of compounds 110 and 111 provided definitive proof that an ester substituent at the 4-position of paclitaxel is necessary for its activity. The crucial importance of
the C-4 acetyl group for the biological activity of taxol and taxotere was proved by the studies of Datta et al.\textsuperscript{87} and Neidigh et al.\textsuperscript{88} C-4 aziridine analogues of paclitaxel 112-114 were evaluated in a tubulin polymerization assay and an in vitro cytotoxicity assay against HCT-116 tumor cell lines.\textsuperscript{89} Analogs 113 and 114 exhibited slightly better potencies than paclitaxel in the tubulin assay whereas analog 112 possesses 3-fold weaker activity as compared to paclitaxel. Georg et al.\textsuperscript{90} synthesized 4-deacetyl-4-isobutanoyl taxol 115 which were found to be less cytotoxic than paclitaxel against B16 melanoma cells and less potent if the microtubule assembly assay. Chen and co-workers\textsuperscript{91} synthesized a large number of C-4 esters, carbonates and carbamates, of which some were highly cytotoxic to cancer cells. Some of these analogs 116-119 also possessed activities against
murine H-109 lung carcinoma in vivo. Thus, the C-4 acetyl group seems to be responsible for anchoring hydrophobically clustered conformation in its proper orientation which is essential for activity.

j. Oxetane D-ring modification:

The oxetane ring is susceptible to ring opening by reaction with electrophilic reagents. Kingston et al.\textsuperscript{92,93} studied the reaction of taxol with three electrophilic reagents zinc bromide, triethyl tetrafluoroborate (Meerwein's reagent) and acetyl chloride. Oxetane ring opened analogs 120 and 121 obtained were found to be inactive in both the tubulin depolymerization assay and cytotoxicity evaluation against KB cells in a cell culture assay. Similar analogs

\begin{center}
\includegraphics[width=\textwidth]{images.png}
\end{center}
were also obtained by Wahl et al.\textsuperscript{39} Chemoselective debenzoylation of 7,13-diacetyl baccatin III with tributyl tin methoxide (Bu$_3$SnOMe) in NMP in the presence of lithium chloride furnished an oxetane ring opened analog 122.\textsuperscript{94} Chen et al\textsuperscript{95} studied the reaction of several lewis acids BBr$_3$, TMSBr, SnCl$_4$, TiCl$_4$, BF$_3$.OEt$_2$ on oxetane ring under proteic and aproteic media. Oxetane ring opened analog 123 reported by Kingston et al\textsuperscript{84} was much less active than paclitaxel both in promoting tubulin polymerization as well as in cytotoxicity assay against human CA 46 Burkitt lymphoma cells.

All these results lead to the conclusion that the presence of the oxetane ring involving 4 and 5 positions of taxane skeleton is crucial for maintaining the biological activity. Oxetane ring opening yields products with drastic reduction in both the disassembly and cytotoxic properties\textsuperscript{22b}. Replacement of the oxygen function of the oxetane ring with nitrogen,\textsuperscript{96,97} sulphur and selenium\textsuperscript{98} has also been reported.

\textbf{k. C-14 modified analogs :}

14\textbeta-hydroxy-10-deacetyl baccatin III isolated from Taxus wallichiana Zucc. was proven to possess better water solubility than 10-deacetyl baccatin III because of the presence of an extra hydroxyl group at C-14. Modification of 14\textbeta-OH-DAB furnished analogues 124-127 which possesses strong cytotoxicities against human breast, non-small cell lung, ovarian and colon cancer cells. Analog 125 exhibits better activity than paclitaxel for non-small cell lung cancer (A 549), colon cancer cell lines (HT-29) and substantial activity against an adriamycin
resistant breast cancer cell line (MCF T-R). Attachment of the N-acyl phenylisoserine side chain at C-14 instead of the original C-13 position results in a 10-fold decrease in cytotoxicity.\textsuperscript{99}

\begin{align*}
124. R &= \text{Ph} \\
125. R &= (\text{Me})_3\text{CO} \\
126. R &= \text{Ph} \\
127. R &= (\text{Me})_3\text{CO}
\end{align*}

1. **A-ring modification**:

Only a few chemical transformations of the A-ring without affecting opening of the labile oxetane ring are known. Treatment of 2',7-bis(TES) paclitaxel with methane sulfonyl chloride and triethylamine in dichloromethane and consequent deprotection yielded A-norpaclitaxel \textsuperscript{128} which was found to be almost as active as paclitaxel in the tubulin polymerization assay.\textsuperscript{93} But analog \textsuperscript{128} was proved to be essentially inactive in the KB cytotoxicity assay. A similar rearrangement of taxotere in the presence of trifluoroacetic acid was reported by Wahl \textit{et al.}\textsuperscript{39} Chen and co-workers\textsuperscript{51} synthesized the A-ring modified analogs \textsuperscript{129} and \textsuperscript{130} which showed a notable loss of cytotoxicity. However, their tubulin assembly activity was superior to taxol. Nor-seco taxol \textsuperscript{131} and nor-seco taxotere \textsuperscript{132} exhibits 40 times weaker activity than paclitaxel against several...
cancer cell lines. Appendino and collaborators observed that MnO₂ oxidation of 7-TES-10-DAB-III furnished the A-nor-B-homo taxoid analog 133. Kingston et al synthesized amide-linked A-norpaclitaxel analogs 134-136 which were significantly less cytotoxic than paclitaxel. The most cytotoxic of these analogs 136 was less active in the tubulin assembly assay than paclitaxel. Nor seco taxoid analog 137 (C-13-N-Me amide linkage) showed reduced cytotoxicity than paclitaxel against several cancer cell lines although it retained a certain level of cytotoxicity. However, the C-13-N-H amide linked analogs 138a-d were virtually inactive.
m. Ring B modification:

The few taxane derivatives that incorporate a modified ring B have arisen from new isolates such as transannular product bearing a C-3/C-11 bond or from the known rearrangement of ring A via activation of the C-1 hydroxyl group. Ring B contracted analog 139a, b was obtained from the reaction of 9-dihydrotaxane derivative with triflic anhydride and subsequent deprotection. The paclitaxel analog 139a exhibited 40 fold less activity than paclitaxel against several tumor cell lines while the docetaxel analog 139b exhibited nearly equal potency to paclitaxel. Chordia et al reacted 13-deoxy-13β-chloro baccatin III with sodium azide in DMF and a trace of water to furnish a B-seco derivative 140 where the C-10/C-11 bond was cleaved. Cleavage of the C-1/C-2 bond was attained by reaction with MnO₂ in CH₂Cl₂ to furnish the B-seco derivative 141.
n. C-ring modification:

Bouchard et al\textsuperscript{36} reported the preparation of a C-ring rearranged taxoid 19-nor-7β,8β-methylene taxoid 142 which was proved to be completely inactive as an inhibitor of microtubule disassembly and displayed no cytotoxic effect against P388 leukemia cell line. Kingston and co-workers\textsuperscript{106} synthesized C-nor paclitaxel analogs 143, 144 and C-seco paclitaxel analog 145 from 2'-TBDMS-6α-hydroxy-7-epi paclitaxel by treatment with lead tetra-acetate and sodium bicarbonate in dichloromethane. Analog 143 was found to be significantly less cytotoxic and less effective at promoting the assembly of microtubules than paclitaxel while analogs 144 and 145 are even less active. Nicolaou et al\textsuperscript{107} and Danishefsky et al\textsuperscript{108} synthesized novel C-aryl taxanes. C-6,7-α-diol paclitaxel analog on treatment with tetrafluoro ammonium borate yielded a C-ring contracted analog 146 which was found to be devoid of any biological activity.\textsuperscript{109} Kingston and collaborators\textsuperscript{110} also reported the synthesis of C-nor paclitaxel.
anallogues 143, 146, 147 and the C-nor-D-seco analog 146. Analog 143 was somewhat less cytotoxic and significantly less effective at promoting the assembly of microtubules than paclitaxel while analogues 144 and 147 are even less active. These results indicate that changes in the size and conformation of the ring C and the attached oxetane ring makes a significant difference to the activity of paclitaxel.

2. Side chain modification:

Structure-activity relationship studies have shown that the C-13-N-benzoyl phenylisoserine side chain of paclitaxel is crucial for the molecule to elicit its biological activities. Also of importance is the stereochemistry at the C-2' and C-3' stereogenic centers, with the most active diastereomer being that
which is found in the natural product.\textsuperscript{111} Conformational studies on paclitaxel suggests that the C-13 side chain has a high degree of freedom and therefore adopts a variety of conformations.\textsuperscript{112} Owing to its important role in the binding of taxol to microtubules, the side chain was also a target of intensive molecular modeling and NMR studies.\textsuperscript{23,113a,b} The modifications of the side chain have been extensively reviewed.\textsuperscript{114,115} 13-epi-paclitaxel where the orientation of the side chain was modified was found to be 20 times less potent than paclitaxel in microtubule binding assay.\textsuperscript{116} Jayasinghe \textit{et al}\textsuperscript{117} reported the synthesis of a one carbon homologated C-13 side chain analog 148\textsuperscript{a,b}. These analogs were found to be 27 times less potent than paclitaxel in the microtubule assembly assay. The inability of these homologs to induce microtubule formation may be due to unfavorable solution conformations, preventing productive interactions with the taxol binding site on microtubules. Chen and collaborators\textsuperscript{118} synthesized C-13-amido-paclitaxel analogs 4-deacetyl-13-amido paclitaxel 149, 13-amido paclitaxel 4-(methyl carbonate) derivatives 150\textsuperscript{a,b} and 13-amido paclitaxel 151. None of these analogs were found to be bioactive in vitro.

\textbf{148} \textsuperscript{a} R = PhCO  
\textbf{b} R = (CH\textsubscript{3})\textsubscript{3}CO  

\textbf{149} \textsuperscript{a} R\textsubscript{1} = Ph, R\textsubscript{2} = Bz, R\textsubscript{3} = H  
\textbf{150} \textsuperscript{a} R\textsubscript{1} = Ph, R\textsubscript{2} = Bz, R\textsubscript{3} = CO\textsubscript{2}Me  
\textbf{b} R\textsubscript{1} = 2-furyl, R\textsubscript{2} = Bz, R\textsubscript{3} = CO\textsubscript{2}Me  
\textbf{151} \textsuperscript{a} R\textsubscript{1} = Ph, R\textsubscript{2} = Bz, R\textsubscript{3} = Ac
Studies directed at elucidating the minimal structural requirement for the C-13 side chain have shown that the hydroxyl group at C-2' is essential for maximum activity. Kant et al and Greene et al in separate studies synthesized 2'-methyl paclitaxel 152 and docetaxel 153 analogues which were found to be more cytotoxic than the parent compound against HCT 116 human colon carcinoma cell lines. These analogues also displayed increased (1.5 fold) binding affinity to microtubules compared to paclitaxel. Prompted by these encouraging results, Greene et al have recently synthesized C-2' hydromethyl derivative 154 of docetaxel. But this compound on biological evaluation was found to be inactive. Uoto and co-workers observed that 2',2'-difluoro docetaxel was 3-10 times more cytotoxic than docetaxel. Cabri et al were successful in synthesizing 2'-epi paclitaxel 155 from paclitaxel.

Investigation on the structural requirements for activity at the C-3' position of taxol showed that the 3'-phenyl ring was not essential for bioactivity, heteroaromatic rings, alkyl and alkenyl groups can serve as replacements. Presence of an oxygen atom at C-3' position leads to less active compounds.
heteroaroyl analogues 156-160 on biological evaluation revealed that the 3'- (2-furyl) paclitaxel analog 159 and 3'- (2-pyridyl) paclitaxel analog 156 were more cytotoxic against B16 melanoma cell line than paclitaxel. The 3'-pyridyl 157 and 3'-furyl 160 analogues were quite active in the tubulin assembly assay but their cytotoxicity against B16 melanoma cells was reduced in comparison to paclitaxel.126 Georg et al127 and Ojima et al128 synthesized various C-3' phenyl analogues Bourzat and co-workers129 prepared para-substituted 3'-phenyl docetaxel analogues 161-168 which on biological evaluation leads to the conclusion

that substituents small in size were better tolerated than bulky substituents on cytotoxicity and microtubule depolymerization properties. Ojima and collaborators130 synthesized several C-3' fluorine analogues 169-174 which were found to be cytotoxic against several cancer cell lines. Georg et al126 synthesized novel N-debenzoyl-N-heteroaroyl paclitaxel and docetaxel analogues 175-179. The 3'-furyl analog 179 showed approximately 2-fold greater activity than
paclitaxel in both microtubule assembly assay and cytotoxic activity against B16 melanoma cells. 2-furyl analog 178 was slightly more active in the microtubule assembly assay and as cytotoxic as paclitaxel against B16 melanoma cell proliferation. Recently Chen and co-workers\textsuperscript{131} prepared 3\textsuperscript{'-}(t)-butylamino carbonyloxy paclitaxel and docetaxel analogs 180 and 181 where analog 180 was 1.5 fold and 3.3 fold less potent than paclitaxel in the tubulin polymerization assay and in the in vitro cytotoxicity assay respectively. Analog 181 was found to be slightly less cytotoxic than 180.
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RESULTS AND DISCUSSIONS

Introduction:

In December 1992, the United States Foods and Drugs Administration (FDA) approved taxol (Paclitaxel) for the treatment of cisplatin refractory metastatic ovarian cancer and in April 1994, for the treatment of breast cancer. However, the yield of taxol from *Taxus* spp., after a tedious and costly isolation procedure, is very low. It has severe water solubility problem for effective drug delivery and therefore, requires elaborate secondary treatment. The production of taxol from the slow growing yew trees leads to problems of environmental consideration as well as debatability on the abundance of the yew trees. Because of all these and other inherent hurdles associated with taxol as drug, intensive search for suitable taxol analogues has already been initiated. There is a clear indication that more and more emphasis is being given, in recent years, for production of 10-DAB III, from which a wide range of semi-synthetic taxol analogues such as taxotere 2 or protax 3 can be made. Already, a large number of analogues of taxol have been prepared and their structure-activity relationship established. Since, the modification of the A-ring at C-16 and C-15 is yet to be accomplished, experiments were envisaged to modify these positions of 10-DAB. Herein, the modifications at C-1, C-16, C-15 of the A ring of this complex diterpene via the manouvring of the C-11/C-12 double bond to get a novel class of taxoids is described.
The C-11/C-12 olefin present in the A ring of Paclitaxel is very interesting due to the fact that, the two planar sp² carbon atoms lock this ring into a pseudo-boat like conformation which contributes to the cage or cup like conformation of the diterpene ring system.²,³ The A-ring, also has a significant role in positioning the acyl groups (benzoyl and acetyl) at C-2 and C-4 along with the N-benzoyl-3-phenylisoserine side chain at C-13 for the right course of biological activity.⁴,⁵ Thus, synthetic manipulation at C-1, C-16 and C-15 of the A ring would allow for a significant change in the overall conformation of the taxane system.
Sometimes back it was shown that tetrasubstituted olefins in sesquiterpene lactone, having -OR (R=H or OAc) functionality at allylic position, undergo rearrangement by the action of m-CPBA. Since the allylic position of C-11, C-12 double bond in 10-DAB III is also substituted by -OR functionality, it was surmised that, it should result in the formation of rearranged products, on treatment with m-CPBA. Taking this lead and also due to the availability of 10-DAB III 4b from Taxus baccata brought from Arunachal Pradesh, experiments were designed to use this compound as starting material for possible transformations of it into A-ring rearranged products leading to the modifications at C-1, C-16, C-15 position of the taxane ring. Thus, when 10-DAB III was exposed to m-CPBA or MgMPT, it furnished a mixture of five rearranged products A, B, C, D and E which were separated by preparative TLC (Ethyl acetate:Pet.ether, 1.5:1).

The compound A was analyzed for C_{29}H_{36}O_{11} by elemental analysis and EIMS which gave molecular ion peak at 560. In the \textsuperscript{1}H NMR spectrum, the single proton multiplets at \(\delta\) 4.22, 4.20, 4.03 and 3.98 ppm were assigned to H-13, H-20a, H-20b and H-5 respectively. Other single proton multiplets at \(\delta\) 3.72, 3.33, 2.52 and 2.32 were assigned to H-6 and H-14 respectively. Aromatic signals at \(\delta\) 8.01, 7.53 and 7.41 indicated that the benzoyl group at C-2 remained intact. The doublet with J=6Hz at \(\delta\) 5.62 and 3.94 integrating to one proton each may be assigned to H-2 and H-3. However, appearance of a two proton signal at \(\delta\) 6.39 ppm and disappearance of one methyl signal compared to the \textsuperscript{1}H NMR spectrum of 10-DAB III, strongly suggested that the C-17-methyl migrated to C-11 and C-16-methyl transformed into methylene with the elimination of a proton.
Thus, the structure of this compound was established as 5. This was also supported by the fact that the signal of H-10 remains as singlet at δ 5.28 ppm and there is no signal for methyl at double bond in its $^1$H NMR spectrum. The structure was further confirmed as 5 by its $^{13}$C NMR spectrum recorded at 75 MHz.

![Structure of Compound 5](image)

Compound B was analyzed for C$_{29}$H$_{34}$O$_{10}$ by elemental analysis. In the IR spectrum it revealed the presence of one α,β-unsaturated system ($v_{\text{max}}$ 1680 cm$^{-1}$), one ketone and one acetate, one benzoyl group and hydroxyl group. In the $^1$H NMR spectrum of compound B, five three proton signals, recorded at δ 2.20, 1.82, 1.62, 1.19 and 1.05 were indicative of OAc and methyls respectively. Thus, it was clear that in compound B, no skeletal modification took place by the action of the per acid. However, the singlet signal at about δ 6.10 ppm (vide: Table 1) or doublet at δ 5.73 (J=4 Hz) for the proton (H-10) was not observed in the $^1$H NMR spectrum of it. In the $^{13}$C NMR spectrum, signal for an additional carbonyl carbon appeared at δ 185.10 s. Both these observations indicated that the hydroxyl group at C-10 has been converted into a keto group. Thus, the structure of compound B was assigned as 6. In the $^1$H NMR spectrum the two doublets at δ 5.70 ppm (J=6Hz) and 3.50 (J=6Hz) were assigned to H-2 and H-3.
respectively. The multiplets at δ 4.40-4.10 ppm integrating to four protons were assigned to H-13, H-20 and H-5. The two proton multiplet at δ 2.10 ppm was assigned to H-14.

![Chemical structure of Compound C](image)

**Compound C** obtained as a solid, m.p. 206°C, was analyzed for C_{29}H_{34}O_{10} by elemental analysis. It was characterized as 7b on the basis of its identical m.p, mixed m.p and spectral data (IR, FABMS and NMR) with that of the authentic compound already reported.  

![Chemical structure of Compound D](image)

7a. R = Ac  
7b. R = H  

The fourth compound **D** having molecular formula C_{29}H_{34}O_{10} was obtained as a gum. Its ^1H NMR spectrum displayed five singlets at δ 1.94, 1.79, 1.59, 1.18 and 1.13 integrating to three protons each. The singlet at δ 5.12 ppm integrating to one proton was assigned to the proton under hydroxyl group at C-10. The single proton doublets at δ 5.51 and 3.59 with J=6Hz along with the
aromatic signals at δ 8.08, 7.64 and 7.45 ppm were assigned to H-2 and H-3, the former as proton under benzoyl group. The doublets at δ 4.17 and 3.98 ppm with J=9Hz and the multiplet at δ 3.95 ppm all integrating to one proton each were indicative of the intact oxetane moiety. The double doublet at δ 4.36 ppm with J=10 and 7 Hz was assigned to the proton under the hydroxyl group at C-7. The appearance of two broad singlets at δ 6.55 and 6.39 ppm each integrating to one proton suggested that some change in the carbon skeleton has taken place. The IR spectrum displayed strong absorption bands at 1725, 1710 and 1685 cm⁻¹. This in conjunction with the ¹H NMR data of it and comparison with those reported for various 10-DAB III derivatives (vide: Table 1) led to the assignment of the structure 8 for the compound D. The ¹³C NMR spectrum displayed signals at 153.6 d, 128.7 d, 202.22 s, 170.14 further confirming the structure 8 for this compound.

![Chemical Structure](image)

The (+) FAB mass spectrum of compound E gave the highest peak at m/z 579 and 562, thus indicating that the elements of water had been added to the transient species 10 and therefore structure 9 was assigned to it. In the ¹H NMR spectrum, one proton doublet at δ 5.70 and 4.13 ppm with J=5Hz were assigned to H-2 and H-3 respectively. The doublets at δ 4.28 and 4.17 ppm with
J=8.5Hz were assigned to H-20. The double doublets at δ 4.31 (J=12,7 Hz), 4.24 (J=6,7 Hz) and doublets of doublets of doublet at δ 2.53 (J=12,16,8 Hz), 2.38 (J=7,16,8 Hz) each integrating to one proton were assignable to H-7, H-13 and H-6a, H-6b respectively. The low field doublets (one proton) at δ 4.90 ppm was assigned to H-5. The one proton singlet at δ 4.38 and the singlets at δ 2.12, 1.86, 1.33, 1.12 and 1.02 integrating to three proton each, were assigned to H-10, OAc, H-19, H-18, H-17 and H-16 respectively. Thus, the structure was fully supported by its NMR spectrum. The singlet signals at δ 141.48 and 134.42 ppm for C-12 and C-11 observed in the 13C NMR spectrum of 10-DAB III were not recorded in the present compound, instead two signals at δ 88.54 and 79.63 ppm appeared, further supporting the structure 9.

The mechanism of the formation of the above mentioned five products from 10-DAB III is similar to the mechanism of peracid epoxidation proposed by Bartlett. However, in this case, the electron pair from oxygen of peracid, perhaps, could not get transferred (dotted line) due to the presence of allylic OH or OAc group and also because of the rigidity of the ring system. As a result, the transient carbocation 10a or 10b rapidly rearranges to different products, among which the deprotonation of the α-hydrogen is the predominating path leading to the formation of 13-keto-10-DAB III 7b (Scheme-1).
It has been reported that 60% \textit{m}-CPBA oxidation of baccatin III 4a and 10-deacetyl baccatin III 4b, gives compound 7a and 7b respectively by allylic oxidation of C-13 OH group. We strongly believe and it is also plausible that these oxidations follow the same course of reaction path as described in Scheme-2.
Scheme-2
NMR data of some known 10-DAB III derivatives

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<th>12(^10)</th>
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<td>(^13)C NMR</td>
<td>(^1)H NMR</td>
</tr>
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<td>-</td>
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Cold peaks: 0.60 m  5.3  0.95 m  6.7
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EXPERIMENTAL

Extraction and Isolation of 10-deacetyl baccatin III from Taxus baccata.

The air dried leaves, stems and bark of the plant Taxus baccata (1.5 Kg) collected from Arunachal Pradesh was grounded and the plant matter was immersed in MeOH for 7 days. The solvent was then concentrated under reduced pressure. 500 ml of water was added to the crude extract. It was then defatted with (3x300 ml) of Pet. ether. The aqueous methanol layer was next extracted with CHCl₃ (5x250 ml). The solvent was evaporated under reduced pressure to yield 52 g of a gummy residue which was purified by repeated column chromatography. A column was packed with a slurry of 500 g of silica gel in (1:5, EtOAc:Pet.ether) and the compound loaded on it. 200 ml fractions on elution were collected in the following order:

Fr 1-5 (1:5, EtOAc : Pet.ether), Fr 6-10 (1:2, EtOAc : Pet.ether), Fr 11-15 (1:1, EtOAc : Pet.ether), Fr 16-20 (EtOAc), Fr 21-25 (1:15, MeOH : EtOAc), Fr 26-28 (1-10 MeOH : EtOAc), Fr 29-31 (1:5, MeOH : EtOAc), Fr 32-35 (1:2, MeOH : EtOAc), Fr 36-40 (1:1, MeOH : EtOAc), Fr 40-45 (MeOH).

Fractions 6-20 were found to contain taxol in comparison with authentic sample on TLC and fractions 21-35 were found to contain 10-deacetyl baccatin III. Fractions 21-35 were combined together and rechromatographed over 500 g of silica gel packed with a slurry in (2:1, EtOAc : Pet.ether). 200 ml fractions were collected in the following order:

Fractions 28-40 were found to contain 10-deacetyl baccatin III on TLC comparison with the authentic sample. These fractions were combined together and further rechromatographed over a 250 g silica gel column packed with a slurry in (1:5, CH₃COCH₃ : CHCl₃). 150 ml of 35 fractions were collected and fractions (15-25) were found to contain 10-DAB III.

Fractions 15-25 were combined together to yield 1.9 g of a gummy residue containing 10-DAB. It was purified by preparative TLC (1:2:1, CH₃CN:CHCl₃: Hexane) to furnish 200 mg of pure 10-DAB III 4b which was recrystallized from acetonitrile.

IR : 3465, 1720, 1245, 1100, 700 cm⁻¹

¹H NMR (DMSO, 300 MHz) : 8 ppm 5.40 d (H-2, J=6.9Hz), 5.21 br s (H-13, OH), 5.13 d (H-10, J=2.4Hz), 5.01 br s (H-7, OH), 4.90 br d (H-5, J=8.9Hz), 4.78 br s (H-10, OH), 4.62 m (H-13), 4.34 s (H-10), 4.09 m (H-7), 4.02 s (H-20), 3.81 d (H-3, J=6.9Hz), 2.28 m (H-6a), 2.20 s (OAc), 2.15 dd & 2.40 dd (2H, H-14, J=9Hz), 1.90 s (H-18), 1.64
m (H-6b), 1.51 s (3H, H-19), 0.94 s (3H, H-17), 0.93 s (3H, H-16).

\[
^{13}C \text{ NMR (75 MHz)} : 210.25 \text{ s (C-9)}, 141.48 \text{ s (C-12)}, 134.42 \text{ s (C-11)}, 169.48 & 22.25 q (\text{Ac}), 165.18 \text{ s}, 133.12 \text{ s}, 130.25 \text{ s}, 129.45 \text{ d}, 128.60 \text{ d (PhCOO)}, 83.70 \text{ d (C-5)}, 80.03 \text{ s (C-4)}, 76.87 \text{ s (C-1)}, 75.40 t (C-20), 74.78 \text{ d (C-2)}, 74.32 \text{ d (C-10)}, 70.88 \text{ d (C-7)}, 66.01 \text{ d (C-13)}, 56.99 s (C-8), 46.47 \text{ d (C-3)}, 42.40 \text{ s (C-15)}, 36.52 \text{ t (C-6)}, 39.18 t (C-14), 26.70 q (C-16), 20.11 q (C-17), 14.75 q (C-18), 9.66 q (C-19).
\]

MS (cims) : 562 [(M+NH\textsubscript{4})]^{+}

Analysis for C\textsubscript{29}H\textsubscript{36}O\textsubscript{10} Requires C 63.96% H 6.66%

Found 63.92% 6.62%

Reaction of 10-DAB with \textit{m}-CPBA:

To a solution of 55 mg of 10-deacetyl baccatin III in 6 ml of dry CH\textsubscript{2}Cl\textsubscript{2} was added 300 mg of \textit{m}-CPBA and stirred overnight. The reaction was monitored on TLC. On completion, it was diluted with 150 ml of ethyl acetate and washed successively with dilute solutions of potassium iodide, sodium thiosulphate and sodium bicarbonate. Finally, after washing with water it was dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure to furnish a crude residue which was purified by preparative
TLC (EtOAc:Pet.ether, 1.5:1) to yield five products 5 (10 mg), 6 (3 mg), 7b (20 mg), 8 (5 mg) and 9 (6 mg).

Spectral data of 5:

\[
\begin{align*}
\text{IR} & : 3400, 1725, 1710, 1640, 1430, 1050, 975 \text{ cm}^{-1} \\
\text{\textsuperscript{1}H NMR} & : \delta \text{ ppm 8.01 m, 7.53 m, 7.41 m (OBz), 6.39 s (H-16, 2H), 5.62 d (H-2), 5.28 s (H-10), 4.89 dd (H-7), 4.22 m (H-13), 4.20 m (H-20a), 4.03 m (H-20b), 3.98 m (H-5), 3.94 d (H-3), 3.72 m, 3.33 m (H-6), 2.52 m, 2.32 m (H-14), 2.12 (OAc), 2.05 (H-19), 1.66 (H-18), 1.19 (H-17).} \\
\text{\textsuperscript{13}C NMR} & : \delta \text{ ppm 213.14 (C-9), 172.3, (OAc), 168.07 (COPh), 154.51 (C-15), 133.66, 129.84, 129.62, 128.77 (OBz), 116.2 (C-16), 84.85 (C-5), 80.69 (C-4), 80.26 (H-2), 80.07 (C-12), 79.89 (C-1), 76.35 (C-20), 72.80 (C-10), 72.34 (C-13), 71.86 (C-7), 55.86 (C-8), 46.44 (C-11), 43.82 (C-3), 40.14 (C-14), 37.17 (C-6), 22.68 (OAc), 22.28 (H-18), 15.66 (H-17), 9.27 (H-19).}
\end{align*}
\]

Analysis for C_{29}H_{36}O_{11} Requires C H

\[
\begin{align*}
\text{Requires} & : 62.13\% \quad 6.47\% \\
\text{Found} & : 62.10\% \quad 6.45\%
\end{align*}
\]

Spectral data of 6:

\[
\begin{align*}
\text{IR} & : 3450, 1725, 1710, 1680, 1465, 1060, 980 \text{ cm}^{-1}
\end{align*}
\]
\[ ^1H \text{NMR} : \delta \text{ ppm 8.47 m, 7.59 m, 7.46 m (OBz), 5.70 d (H-2, J=6Hz), 5.20 m (H-7), 4.40-4.10 m (H-13, H-20, H-5), 3.50 d (H-3, J=6Hz), 2.30 m (H-6), 2.20 s (OAc), 2.10 m (H-14), 1.82 s (H-18), 1.62 s (H-19), 1.19 s (H-17), 1.05 s (H-16).} \]

\[ {^{13}C \text{NMR} : \delta \text{ ppm 201.78 s (C-9), 185.10 s (C-10), 172.30 s (OAc), 157.08 s (C-12), 149.13 s (C-11), 167.68 s (COPh), 133.80 d, 130.25 d, 129.49 s, 128.80 d (OBz), 84.85 d (C-5), 80.91 s (C-4), 78.70 d (C-2), 76.42 t (C-20), 74.94 s (C-1), 72.76 d (C-7), 63.35 d (C-13), 57.49 s (C-8), 46.10 d (C-3), 42.70 s (C-15), 37.17 t (C-6), 36.25 t (C-14), 24.53 q (C-16), 22.77 q (Ac), 22.53 q (C-17), 21.56 q (C-19), 21.17 q (C-18).} \]

Analysis for C\textsubscript{29}H\textsubscript{14}O\textsubscript{10} Requires C H

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Spectral data of \textit{7b}:

M.p. : 206°C

IR (KBr) : 3450, 1725, 1710, 1685 cm\textsuperscript{-1}

\[ ^1H \text{NMR} : \delta \text{ ppm 8.08, 7.63, 7.48 (2t, 1d, J=8Hz), 5.66 d (J=7Hz, H-2), 5.43 s (H-10), 4.95 d (J=9, H-5), 4.26 m (H-7), 4.31 d and 4.14 d (J=9Hz, H-20), 3.98 d (J=7Hz, H-3), 2.68 d, 2.95 d} \]
(J=20Hz, H-14), 2.50 m (H-6), 2.20 s (H-18), 2.10 s (OAc), 1.88 m (H-6), 1.72 s (H-19), 1.24 s (H-17), 1.18 s (H-16).

$^{13}$C NMR : $\delta$ ppm 208.50 (C-9), 199.09 (C-13), 170.12 (OAc), 166.16 (COPh), 157.50 (C-11), 138.55 (C-12), 133.56, 129.70, 129.09, 128.45 (OBz), 84.24 (C-5), 80.55 (C-4), 77.38 (C-1), 76.15 (C-20), 75.65 (C-10), 72.80 (C-2), 71.30 (C-7), 58.44 (C-8), 45.74 (C-3), 43.32 (C-15), 42.70 (C-14), 36.42 (C-6), 32.50 (C-17), 21.35 (COCH$_3$), 17.50 (C-16), 12.94 (C-18), 9.05 (C-19).

(+) FABMS : 543 (MH$^+$)

Analysis for C$_{29}$H$_{34}$O$_{10}$ Requires C H

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Found 64.16% 6.30%

Spectral data of 8:

IR : 3460, 1725, 1710, 1685, 1350, 1000 cm$^{-1}$

$^1$H NMR : $\delta$ ppm 8.08 m, 7.64 m, 7.45 m (OBz), 6.55 br s (H-13), 6.39 br s (H-14), 5.51 d (J=6Hz, H-2), 5.12 s (H-10), 4.36 dd (J=10,7Hz, H-7), 4.17 d (J=9Hz, H-20a), 3.98 d (J=9Hz, H-20b), 3.95 m (H-5), 3.73 (OH), 3.59 d (J=6Hz, H-3), 2.57 m (H-6a), 2.05 m (H-6b), 1.94 s (OAc), 1.79 s (H-19), 1.59 s (H-18), 1.18 s (H-16), 1.13 s (H-17).
\(^\text{13}\)C NMR:  \(\delta\) ppm 209.28 (C-9), 202.22 (C-1), 170.14 (CO\text{CH}_3), 169.75 (COPh), 153.6 (C-13), 132.10, 131.20, 130.12, 128.94 (OBz), 128.7 (C-14), 86.51 (C-5), 80.74 (C-4), 74.65 (C-20), 74.54 (C-12), 71.58 (C-7), 69.68 (C-2), 65.53 (C-10), 50.50 (C-8), 48.93 (C-15), 45.25 (C-11), 40.11 (C-3), 36.85 (C-6), 21.84 (C-18), 21.63 (CO\text{CH}_2), 15.91 (C-16), 12.58 (C-17), 11.27 (C-19).

Analysis for C\textsubscript{29}H\textsubscript{34}O\textsubscript{10}: Requires C H

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Spectral data of 9:

IR: 3400, 1725, 1710, 1465, 1050 cm\(^{-1}\)

\(^1\)H NMR:  \(\delta\) ppm 8.03 m, 7.58 m, 7.47 m (OBz), 5.70 d (J=5 Hz, H-2),

(CDCl\(_3\) + DMSO d\(_6\))  \(\delta\) ppm 4.90 d (J=8 Hz, H-5), 4.38 s (H-10), 4.31 dd (J=12, 7 Hz, H-7),

\(d\) (J=5 Hz, H-3), 3.94 (OH, H-12), 3.84 (OH, H-13), 3.72 (OH, H-11), 2.53 ddd (J=12, 16, 8 Hz, H-6a), 2.38 ddd (J=7, 16, 8, H-6b), 2.42 dd (J=6, 14, H-14a), 2.32 dd (J=7, 14, H-14b), 2.12 (OAc), 1.86 s (H-19), 1.33 s (H-18), 1.12 s (H-17), 1.02 s (H-16).

\(^{13}\)C NMR:  \(\delta\) ppm 211.87 (C-9), 172.79 (CO\text{CH}_3), 170.64 (COPh),
(CDCl$_3$) 133.65, 130.08, 129.37, 128.65 (OBz), 88.54 (C-11), 84.55
DMSO d$_6$) (C-5), 80.90 (C-4), 80.27 (C-1), 79.63 (C-12), 76.77 (C-2), 76.25 (C-20), 73.41 (C-13), 71.86 (C-7), 70.62 (C-10), 58.15 (C-8), 45.25 (C-3), 43.59 (C-15), 37.12 (C-6), 38.33 (C-14), 22.68 (OAc), 21.11 (C-18), 19.33 (C-16), 17.34 (C-17), 9.27 (C-19).

(+) FABMS : 579 [M$^+\cdot$H], 562 [M$^+\cdot$OH]

Analysis for C$_{29}$H$_{38}$O$_{12}$ Requires C H

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Found 60.16% 6.60%
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