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Review

Recent advances in structure modifications of Taxol† (Paclitaxel)

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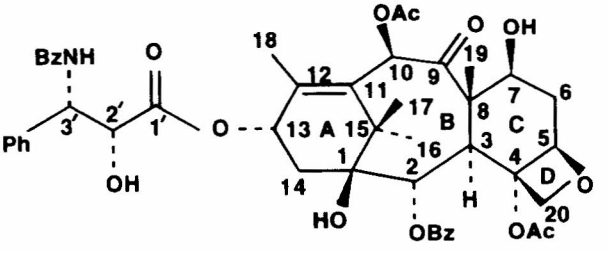
Taxol (paclitaxel), a complex polyoxygenated diterpene isolated originally from the bark of *Taxus brevifolia* is a promising anticancer agent in the treatment of ovarian and breast cancer. The molecule has been extensively modified during the last few years in a bid to enhance its water solubility and to improve its therapeutic profile. The present review gives an account of the recent developments in the structure modifications of taxol and comments on the structure activity relationships of the analogues.

Natural products are the organic molecules which are elaborated by living tissues derived from higher plants, fungi, microbes, marine organisms and animals and exhibit a remarkably wide range of chemical diversity and a multiplicity of biological properties. From time immemorial natural resources have been in use for combating human ailments. Over the last fifteen years interest in drugs of plant origin has been reviving and growing steadily, and the drug researchers are exploring the potential of natural products for the cure of still unsurmountable diseases like cancer and AIDS.



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Cancer is a disease characterised by unregulated proliferation of cells. It is a growing public health menace and more than six million new cases of this disease are reported every year. It was in the year 1960 that a systematic screening programme for antineoplastic agents of plant origin was initiated in National Cancer Institute, USA under Dr J.H. Hartwell. Plant samples collected at random by the US Department of Agriculture were supplied for antitumour screening. During such screening, the bark of Pacific yew, *Taxus brevifolia*, showed activity against a number of cell lines. Using bioactivity-guided fractionation, the active principle, then named taxol, was isolated in 1967 and the structure **1** was elucidated in 1971 by Wani *et al*[1]. Taxol is a novel highly functionalised diterpenoid comprising a taxane nucleus with four ester groups attached to it. It may be named as 5β, 20-epoxy-1, 2α,4,7β,10β, 13α-hexahydroxytax-11-en-9-one-4,10-diacetate-2-benzoate 13-ester with (2*R*,3*S*)-N-benzoyl-3-phenylisoserin. It took more than two decades for taxol to reach the clinics after its discovery. In December 1992, the drug was approved by the US FDA as second line of therapy for platinum-resistant advanced ovarian cancer. Later, in April 1994 taxol was cleared for metastatic breast cancer. The activity profile includes its activity against murine B16,L1210,P388 and P1534 Leukaemias. It is also active against Walker 256 Carcinoma, Sarcoma 180 and Lewis lung tumour cell lines[2]. Taxol has proved efficacious against a number of leukaemias and solid

†When originally discovered the generic name given was taxol, before marketing Bristol-Myers Squibb Co. in United States retained this name as their registered trademark and a new generic name paclitaxel was given. In the present communication, however, the original name, taxol has been used.

tumours in xenografts including those in breast, ovary, brain and lung[3].

The mechanism of action of taxol has been extensively studied[1-13] In precise, the mode of action of taxol involves promotion of polymerization of the tubulin thereby promoting the formation of extremely stable and nonfunctional microtubules resulting in cell death.

The two factors which have prompted medicinal chemists to modify the structure of taxol are the low water solubility (0.03 mg/mL)[14] of this compound thus hampering its formulation, and undesirable side-effects and multidrug resistance. Efforts have been made to prepare analogues with better pharmacological properties and/or activity spectra against various types of tumour. Some excellent reviews covering chemistry and structure- activity relationship studies on taxol have appeared recently[15-19]. The present review gives an account of the recent developments, covering the literature published mainly during the last three years, towards structure modifications of taxol leading to newer taxol analogues and their structure activity relationships. Structure modifications carried out in taxol have been discussed under the titles of modifications in the side chain at C-13, changes in substituents at other positions of taxane nucleus, and changes in taxane skeleton. Photoaffinity analogues of taxol and photochemical and electrochemical modifications of taxol and taxotere have also been covered.

The physical approach to overcome the solubility problem of taxol has been its formulation as a 50% mixture of Cremophor EL (polyethoxylated castor oil) and 50% alcohol. The drug is then diluted with saline and administered at doses of 135-250 mg/m^2 as a 24 hr infusion[18]. The major drawback of the formulation is the hypersensitivity reactions caused by Cremophor EL, which necessitates the use of prophylactic antiallergic premedications, and the adoption of longer infusion schedule (24 hr) rather than short periods. Considerable research is underway to utilise liposome as drug carrier to mitigate the side effects[18].

A good amount of success has been achieved in the synthesis of water soluble taxol analogues by making modifications in its structure particularly in the side chain attached at position 13 of the taxane nucleus.

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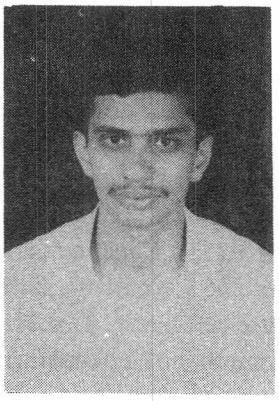
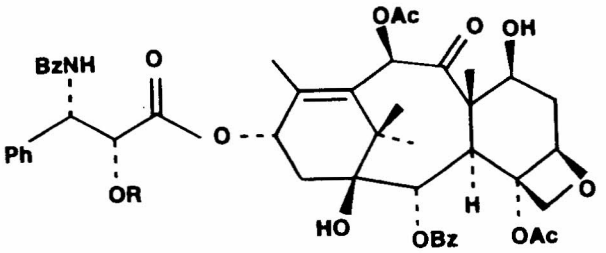
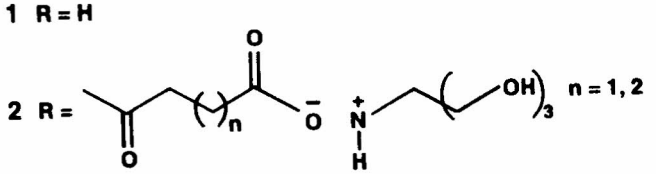
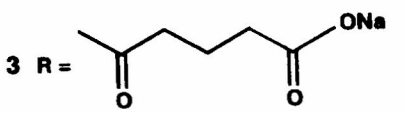


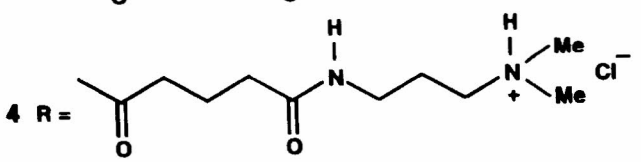
Neeraj Mahindroo completed his M.Pharm. Degree course in Pharmaceutical Chemistry from Panjab University in 1996 after having received his bachelors degree from the same university in 1994. He worked on a selected research project during his post- graduate course, and was a recepient of a research fellowship from the UGC, New Delhi.

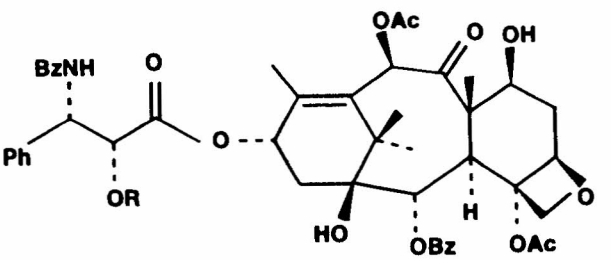


1 R = H





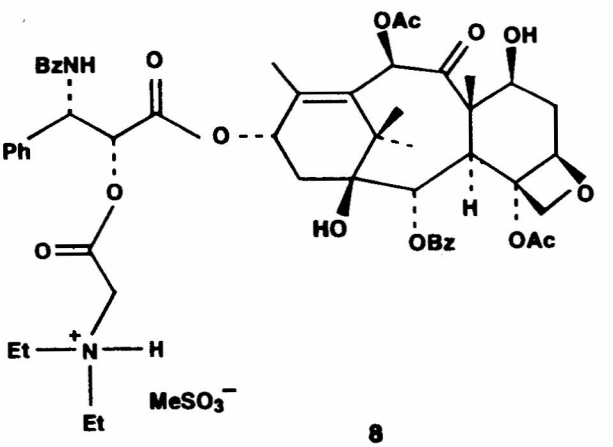




5 R = $COCH_2CH_2CONHCH_2CH_2SO_3^-Na^+$

6 R = $COCH_2CH_2CONHCH_2CH_2CH_2SO_3^-Na^+$

7 R = $COCH_2CH_2SO_3^-Na^+$



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Modifications in the Side Chain at C-13 of Taxol

Deutsch *et al*[20] have prepared several water-soluble esters **(2-4)** of the 2′-hydroxy group with impressive biological action. The compounds exhibited cytotoxicity comparable to or even better than taxol in assay with B16 melanoma cells. The compounds, however, suffer from tendency to release taxol rapidly in aqueous media causing precipitation problems[20]. Water-soluble analogues with 2′- hydroxyl group linked through a succinate group to taurine or 3-amino-1-sulphopropionic acid **(5-7)** have been prepared by Kingston *et al*[21]. These compounds have somewhat reduced activity as compared to taxol though there is 100-200 fold increase in water solubility.

Stella *et al*[22] have reported to preparation of methane sulphonate salts of the derivatives of taxol, such as **8**, with amino acids in C-2′ and C-7 positions whose water solubility was greater than 2 mg/mL. Recently, Nicolaou *et al*[23] have designed and synthesised a series of water-soluble taxol- releasing derivatives **(9-18)** (protaxols) with improved pharmacological properties. The design of these analogues is based on a proposed mechanism (Figure 1) of

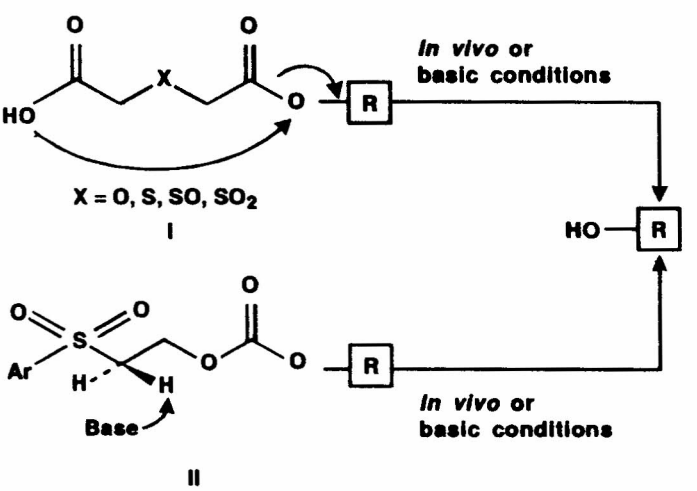
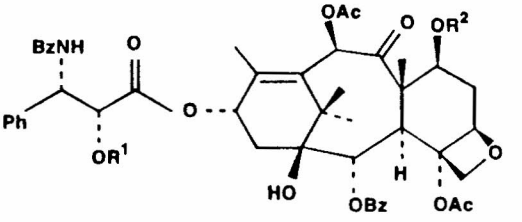
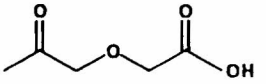
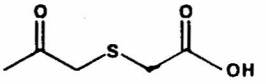
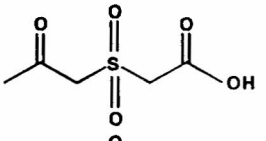
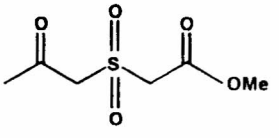
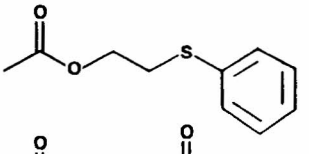
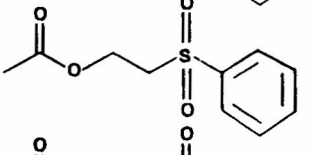
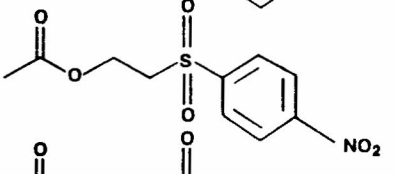
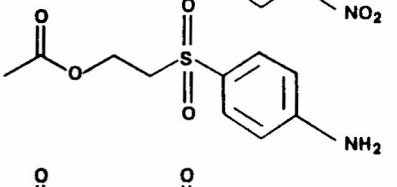
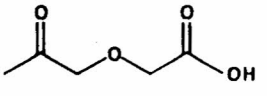
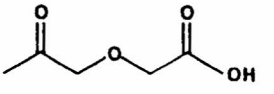
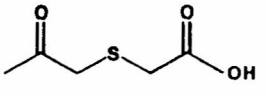
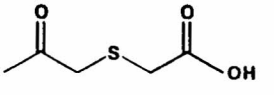
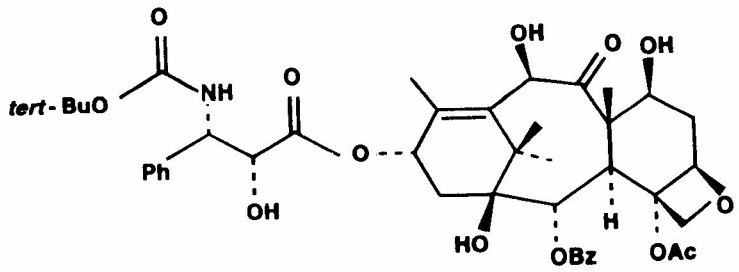


Figure 1--Proposed mechanism of taxol release form designed protaxols; R=taxol residue.



	R^1	R^2	Water solubility (mg / ml)
1	H	H	<<0.10
9		H	0.84
10		H	0.35
11		H	1.20
12		H	–
13		H	–
14		H	< 0.10
15		H	< 0.10
16		H	< 0.10
17			0.50
18			0.46



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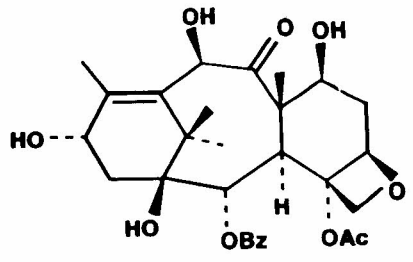

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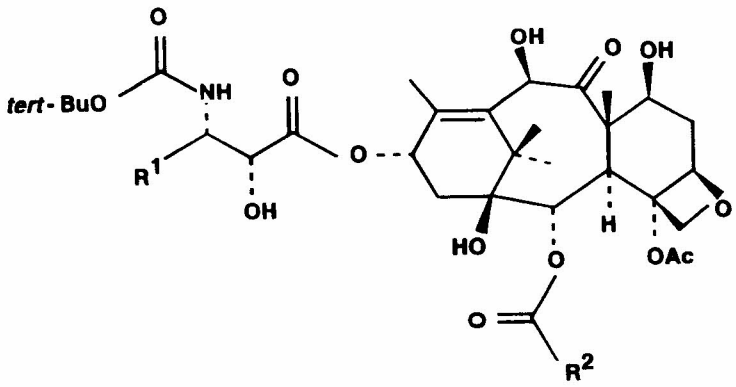
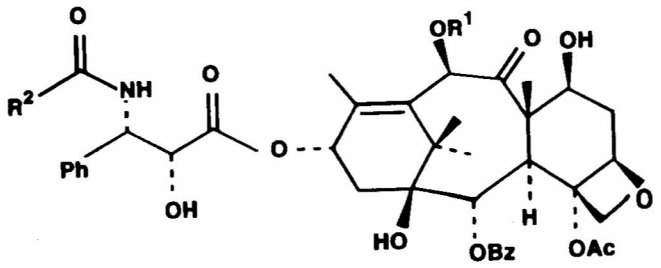


21 $R^1 = C_6H_{11}$, R^2 = Ph
22 R^1 = Ph, $R^2 = C_6H_{11}$
23 $R^1 = C_6H_{11}$, $R^2 = C_6H_{11}$
24 R^1 = *p*-F-Ph, R^2 = Ph

release of taxol from its prodrug. The group substituted at C-2′ to enhance solubility of taxol should either initiate its own cleavage from the conjugate and generate taxol *in situ* **(Type I)** or the activating group should be base-labile moiety as certain drug-resistant tumours have microenvironment of basic *p*H **(Type II).** Type I compounds show considerably high aqueous solubility while Type II show a little improvement in solubility. For Type II compounds, rate of taxol release increases with electron- withdrawing ability of any substituent while for Type I compounds rate of release increases with electron-withdrawing nature of the linking hetero atom. Protaxols have shown potencies similar to taxol against various cell lines including multiple drug resistant ovarian (OVCAR-3), lung (H-322) and leukaemia (MOLT-4) cells. Compound **11** was found to be particularly promising[23].

French workers, Potier *et al*[24] have reported the synthesis of a highly promising taxol analogue named taxotere (RP56976) docetaxel (**19**) which is approximately twice as potent as taxol and more water soluble. Taxotere has been prepared by semi-synthesis from 10-deacetylbaccatin III (C10-DAB **20**) and differs from taxol in having the side chain at C-13 with a *tert*- butoxycarbonyl moiety in place of the benzoyl group and the acetoxy group at C-10 being replaced by a hydroxy group.

Following the success of taxotere, several modifications in the structure of taxotere were carried out. Ojima *et al*[25] modified taxotere at C-3′ of the side chain and C-2′ position of the nucleus. Introduction of one cyclohexyl moiety in taxotere does not affect tubulin binding property. Cytotoxicity of **21** and **22** is eight to twelve times weaker than taxotere against P388 cell lines. Substitution of two phenyl rings at C- 3′ and C-2 positions with two cyclohexyl groups as in **23** results in substantial loss of activity in microtubule disassembly inhibition but cytotoxicity remains the same as for **21** and **22**[25].

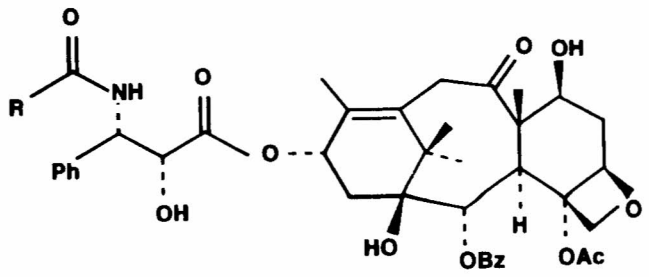


1 R^1 = Ac, R^2 = Ph
25 R^1 = COMe, R^2 = $(Me)_3CO$
26 R^1 = Me, R^2 = $(Me)_3CO$
27 R^1 = CO_2Me, R^2 = $(Me)_3CO$
28 R^1 = COPh, R^2 = $(Me)_3CO$
29 R^1 = COBu, R^2 = Ph
30 R^1 = CO-, R^2 = Ph
31 R^1 = $CON(Me)_2$, R^2 = Ph
32 R^1 = Me, R^2 = Ph
33 R^1 = CO_2Me, R^2 = Ph
34 R^1 = COPh, R^2 = Ph

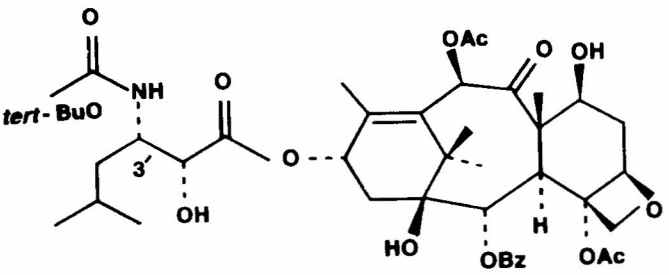
Replacement of C-3′ phenyl with *p*-fluorophenyl with no change in substitution at C-2 gives a very active taxotere analogue **24**. It has an IC_{50} of 0.03 mg/mL *in vitro* against P388 leukaemia cell in comparison to the IC_{50} of taxotere as 0.04 mg/mL[26].

Changes at C-10 position. Analogues **25-28** of taxotere with change in functionality at C-10 displayed cytotoxic properties. Analogues with C-10 methyl ether **(26)** or methyl carbonate **(27)** are more cytotoxic than taxol **1** or 10- acetoxytaxofere **25**. They also exhibit better tubulin binding properties. C-10 modified taxol analogues **29-34** showed tubulin binding similar to taxol but were less cytotoxic than the parent compound except the C-10 carbamate **31**[27]. The 10-acetoxy group makes only a small contribution to the activity of taxol while 10-deoxy series accentuates the activity of taxotere. This was proved by the fact that 10-deacetoxytaxol **35** showed ED_{50} equivalent to that of taxol while 10-deoxytaxotere **36** exhibited cytotoxicity better than that from taxotere in the experiments carried out by Kingston *et al*[28]. It can thus be inferred that C-10 acetoxy contributes very little to receptor binding. This observation has been reinforced by studies carried out by Holton *et al*[29] who have reported a simple synthesis of 10-deacetoxytaxol derivatives; the C-10 oxygen substituent can be reductively removed in high yield by reactions of taxol, baccatin III or 10- deacetylbaccatin III with samarium diiodide.

Another analogue **37** of taxol where the benzoyl group was replaced by *tert*-butoxycarbonyl, as in taxotere, and the phenyl at C-3′ by isobutyl group showed superior activity than taxol in both tumour cell line and cytotoxicity assays and *in vivo* studies.



35 R = Ph
36 R = $(Me)_3CO$



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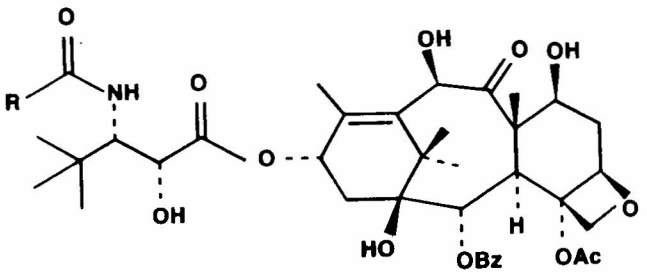
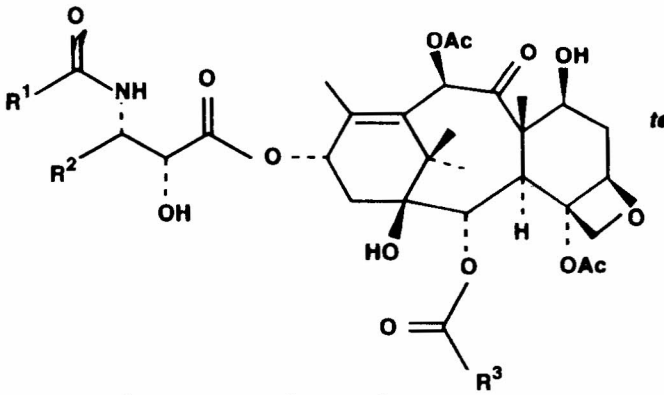
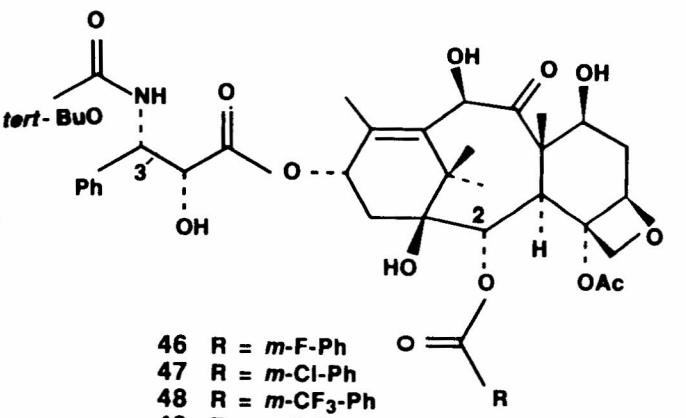


38 R = $(Me)_3CO$
39 R = $Et\text{-}C(Me)_2O$
40 R = $(Me)_3CNH$
41 R = PhNH

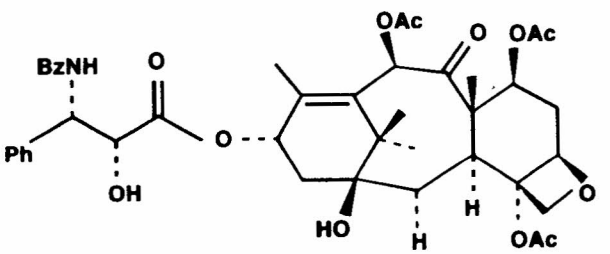
The study also surmised that phenyl ring at C-3′ position is not essential for activity, heteroaromatic ring, alkyl and alkenyl group can serve as replacements. Oxygen at C-3′ leads to a less active compound[30]. Recently Ali *et al*[31] have prepared novel 3′- (*tert*-butyl)-3′-dephenyl analogues of taxol and taxotere with significantly enhanced water solubility properties. The most active derivatives found were the taxotere analogue **38**, its homologue **39**, and the urea analogues **40** and **41**. All the four analogues were found to be more cytotoxic than taxol, and the derivatives **38** and **39** had activity similar to taxotere



42 $R^1 = (Me)_3CO$, $R^2 = Ph$, $R^3 = C_6H_{11}$
43 $R^1 = Ph$, $R^2 = C_6H_{11}$, $R^3 = Ph$
44 $R^1 = C_6H_{11}$, $R^2 = C_6H_{11}$, $R^3 = C_6H_{11}$



46 R = *m*-F-Ph
47 R = *m*-Cl-Ph
48 R = *m*-CF_3-Ph
49 R = *p*-F-Ph
50 R = *p*-MeO-Ph
51 R = *p*-CF_3-Ph



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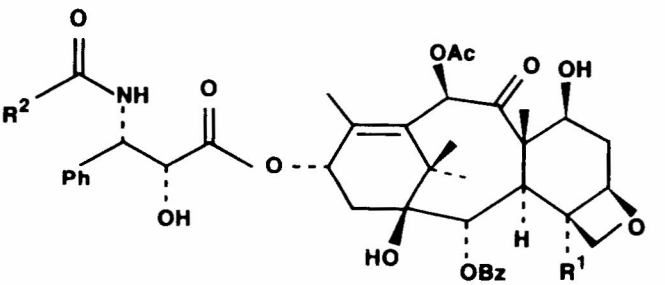


52 R^1 = OH, R^2 = Ph
53 R^1 = OH, $R^2 = (Me)_3CO$
54 R^1 = H, R^2 = Ph

against B 16 melanoma cells. The analogues were about ninety times more water-soluble than taxol and four to five times more soluble than taxotere[31].

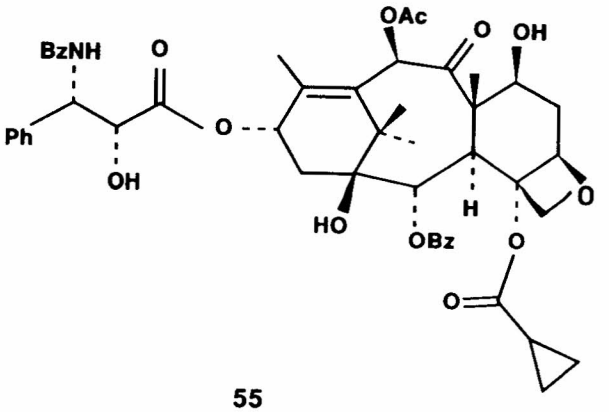
Boge *et al*[32] have carried out modifications at C-3′ and C-2 positions of taxol. Analogues **42,43** and **44** displayed better microtubule assembly and B 16 cytotoxicity as compared to taxol, indicating that none of the aromatic moieties at C-3′ or C-2 are essential for activity. In case of **42**, the population of hydrophobically clustered conformation increases in polar media, so aromaticity of C-3′ ring appears to be a significant driving force in the formation of clustered conformation with C-2 ring having much less effect[32].

The natural stereochemistry (2′*R*,3′*S*) of the C-13 *N*-benzoyl- 3′-phenylisoserine side chain is essential for activity. 2′-Hydroxyl group is required for strong microtubule binding[33]. Homologues of the C-13 side chain have been found to be inactive[34]. The *N*-benzoyl can be widely modified and also the 3′-phenyl moiety can be replaced by aliphatic or heteroaromatic moieties.

Changes at Other Positions of Taxane Nucleus

Changes at C-2 substituents. The α- benzoyloxy functionality present in taxol appears to play an essential role in binding taxol to its receptors, as its removal gives 2- deoxytaxol **45** which shows modest *in vitro* cytotoxicity in human colon cancer cell line. Its *in vitro* ability to polymerize tubulin was also below measurable level[35]. Substitution on *m* - or *p*-position of phenyl ring of the benzoyloxy group of taxotere gave analogues **46** to **51** which showed cytotoxicity comparable to taxotere against P388 leukaemia cell line[36].

Changes at C-4 Substituent. The acetyl group linked to the oxygenated function at C-4 as an ester seems to be responsible for anchoring hydrophobically clustered conformation in its proper orientation which may be essential for activity. This has been demonstrated by Datta *et al*[37] and Kingston *et al*[38], who in separate studies have shown that 4-deacetyltaxol **52** and 10-acetyl-4-deacetyltaxotere **53** have



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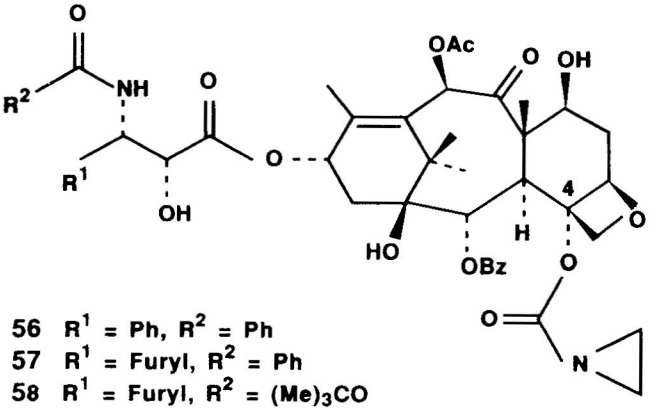
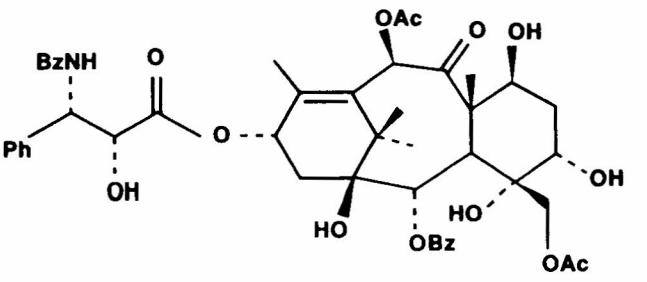


56 R^1 = Ph, R^2 = Ph
57 R^1 = Furyl, R^2 = Ph
58 R^1 = Furyl, R^2 = $(Me)_3CO$



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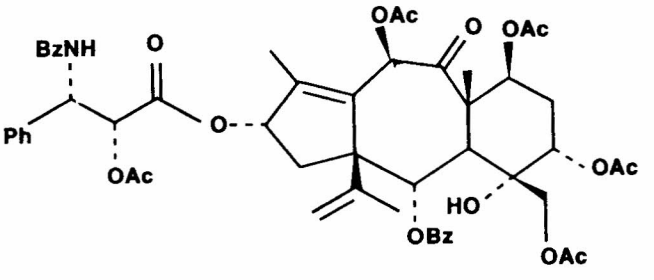

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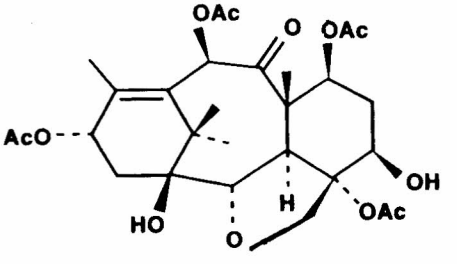


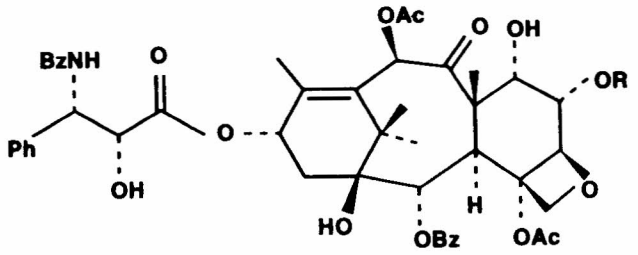
61

very poor activity in the *in vitro* microtubule binding assay, human CA46 Burkitt lymphoma cell assay and tubulin assembly assay Further, a study carried out by Kingston *et al*[39] has shown that complete removal of the oxygenated function as in 4-deacetoxy taxol **54**, results in a drastic reduction in the activity. Compound **54** was found to be much less active than taxol against CA46 Burkitt lymphoma cell and tubulin assembly assay.

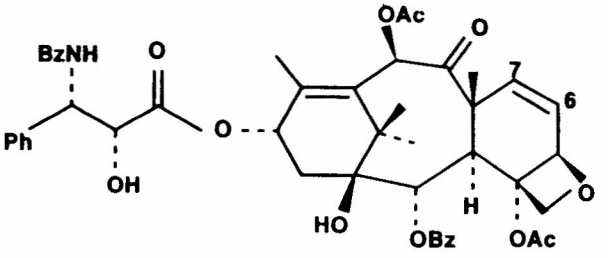
Chen *et al*[40] have synthesised the C-4 cyclopropyl ester analogue **55** of taxol, and in preliminary biological evaluation found it to be more potent *in vitro* than taxol. Prompted by the encouraging results these workers have recently synthesised the analogues **56**, **57** and **58** in which the C-4 cyclopropyl group was replaced with an isosteric aziridine ring with an intention that C-4 aziridine ring-bearing analogue **56** could potentially function as an alkylating agent at the tubulin binding site. The compound, however, was found to possess 3-fold weaker activity as compared to taxol in the tubulin assay. Other aziridine analogues **57** and **58** exhibited slightly better potencies than taxol in the same assay[41].

Presence of oxetane ring involving 4- and 5-positions of taxane skeleton is crucial for maintaining the activity; ring opening leads to a drastic decrease in both disassemble and cytotoxicity[17]. Reaction of taxol with excess triethyloxonium tetrafluoroborate (Meerwein's reagent) led to the product **59** with an opened oxetane ring. The product **60** in which oxetane ring is opened and the ring-A is contracted was obtained when taxol was treated with acetyl chloride. Both the derivatives were found to be inactive in tubulin disassembly assay and cytotoxicity evaluation against KB cells in a cell culture assay[42,43].

A novel taxane structure **61**, in which oxetane ring was not intact and a tetrahydrofuran ring featured,



62 R = H
63 R = MeCO
64 R = PhCO
65 R = *o*-CH_3PhCO
66 R = *cyclo*-C_3H_5CO



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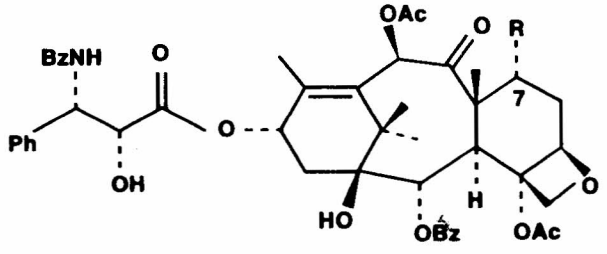
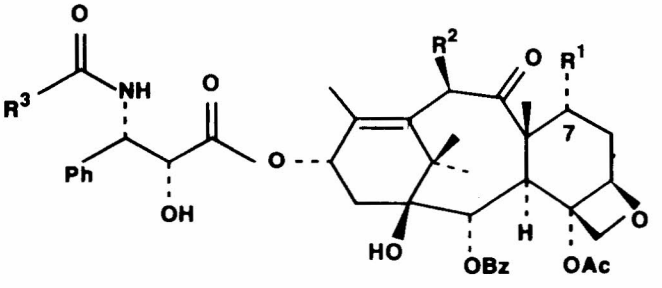


67 R = F
68 R = N_3



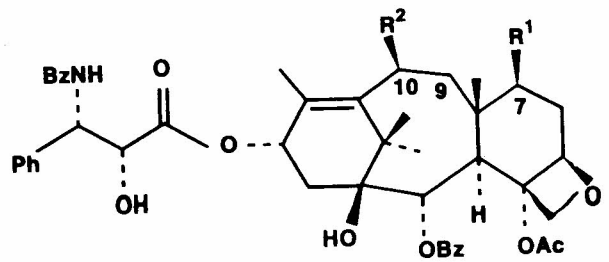
70 R^1 = OH, R^2 = H, R^3 = Ph
71 R^1 = H, R^2 = OH, R^3 = $(Me)_3CO$
72 R^1 = H, R^2 = H, R^3 = $(Me)_3CO$

was obtained when chemoselective debenzoylation of 7,13- diacetylbaccatin was achieved with tributylin methoxide in NMP in the presence of lithium chloride as an activating agent[44].

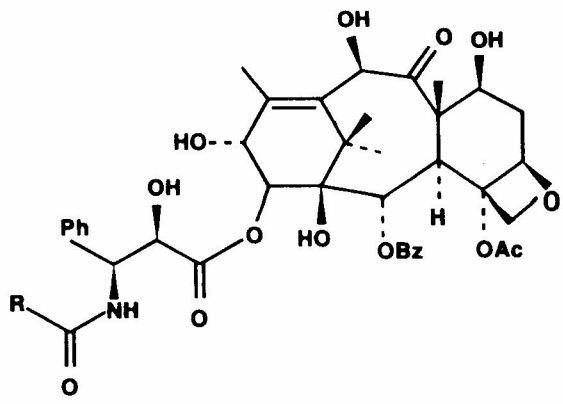
Changes at C-6 position. Addition of any oxygenated substituent of position-6 of taxol leads to analogues **62** to **66**, none of which is as effective as taxol in promoting the tubulin assembly. However, all except **62** and **65** stabilised the polymerised tubulin to the extent equal or better than taxol[45].

Changes at C-7 Substituent. Hydroxy group at position-7 of taxol does not significantly interact with microtubule binding site. This was corraborated by synthesis of 7α- fluorotaxol **67** which showed excellent ability to polymerize tubulin *in vitro* and displayed potent cytotoxicity in HCT-116 cell line [46,47]. However, substitution of C-7 hydroxyl with azido group or with a double bond at 6,7-position leads to 7α-azido- 7-deoxytaxol **68** and 7-deoxy- $\Delta^{6,7}$-taxol **69**, respectively which are not as effective as taxol in promoting the tubulin binding but stabilised polymerised tubulin better than taxol[45]. Chen and co- workers[48] have also observed that C-7 hydroxyl is not involved in binding and C-10 acetate contributes very little to receptor binding as 7-epi-10-deoxytaxol **70** displayed potent activity. 7- Deoxytaxotere **71** and 7,10- dideoxytaxotere **72** showed a high level of cytotoxicity against P388 leukaemia cell and excelled inhibition of disassembly of microtubules, thus, giving the inference that C-7 hydroxyl and C-10 oxygenated function (hydroxy or acetoxy) of taxoids have only secondary effects on the activity[49].

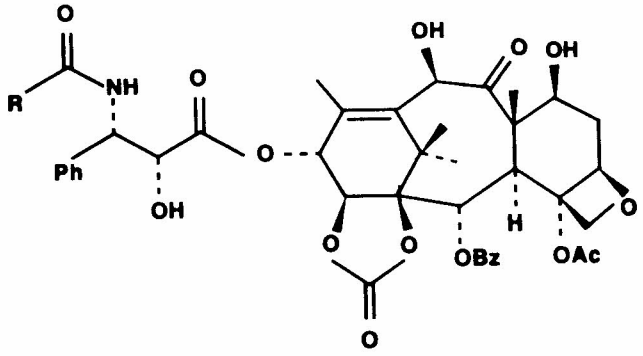
Change at C-9 carbonyl. The removal of C-9 carbonyl function from the taxane skeleton resulted in an equally active 9-deoxotaxol **73**. Simultaneous removal of the oxygenated function at C-7 and C- 9 affording **74** resulted in a little loss of activity, while removal of acetoxy function at C-10 in addition to the removal of carbonyl at C-9 and hydroxy at C-7 gave



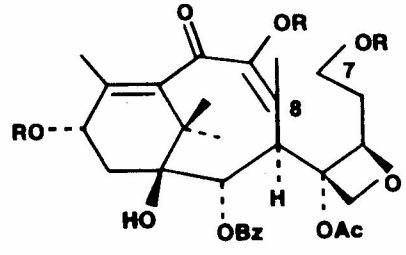
73 R^1 = OH, R^2 = OAc
74 R^1 = H, R^2 = OAc
75 R^1 = H, R^2 = H



78 R = Ph
79 R = $(Me)_3CO$



76 R = Ph
77 R = $(Me)_3CO$



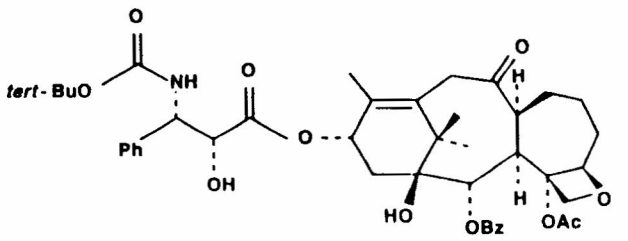
80 R = H
81 R = Ac

10- deacetoxyl-7-deoxy-9- deoxotaxol **75** which was ten times less active than taxol[50].

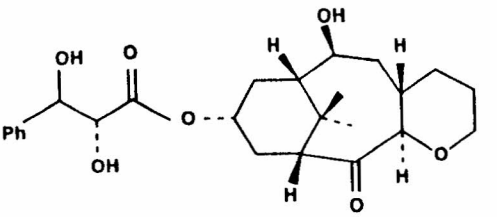
Changes at C-14. Effect on activity of substituting additional oxygenated function at 14-position of deacetylated taxol or taxotere has also been studied. Analogues **76**, **77**, **78** and **79** possess strong cytotoxicity against human breast, non small cell lung, ovarian and colon cancer cells. Compound **77** exhibits activity better than taxol for non small cell lung cancer (A549) and colon cancer cell lines (HF29) and substantial activity against adriamycin resistant breast cancer cell lines (MCF 7-R). These analogues have also shown improved water solubility, bioavailability and hydrophobicity related drug resistance. 14β-Hydroxy-10-acetylbaccatin isolated from *Taxus wallichiana* needles was used as the substrate for these modifications[51].

Changes in the Taxane Skeleton. Appendino *et al*[52] prepared the diterpenoid precursors **80** and **81** of taxol analogues by reduction of the oxidized form of 10-deacetylbaccatin III **20** to circumvent certain restrictions such as inverted cup shape of the taxane skeleton which makes some of functional groups unreactive, for example bridge head double bond.

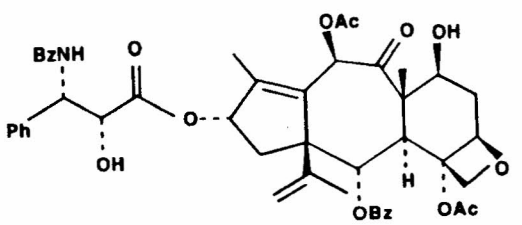
Six-membered C ring of the taxane skeleton is essential for antitumour activity. Its expansion to seven-membered ring results in total loss of activity. The C ring expanded analogue **82** of taxotere was found to be completely inactive as an inhibitor of microtubule assembly and displayed no cytotoxic effect against P388 leukaemia cell line[53]. Introduction of an ether functionality in C-ring by (2+2) photocycloaddition, but maintaining its six-membered character as in analogue **83**, however, results



82



83



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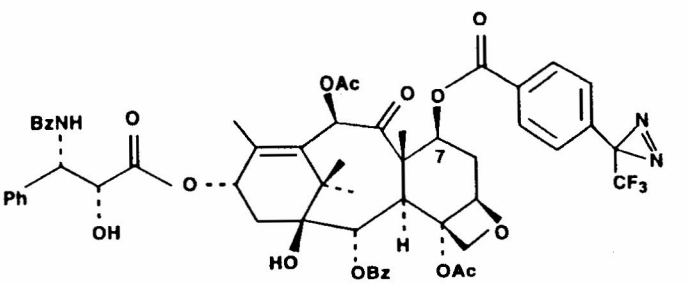


85

in retention of activity. The compound **83** mimics the polarity of C ring and is biologically active as shown by *in vitro* tubulin test[54].

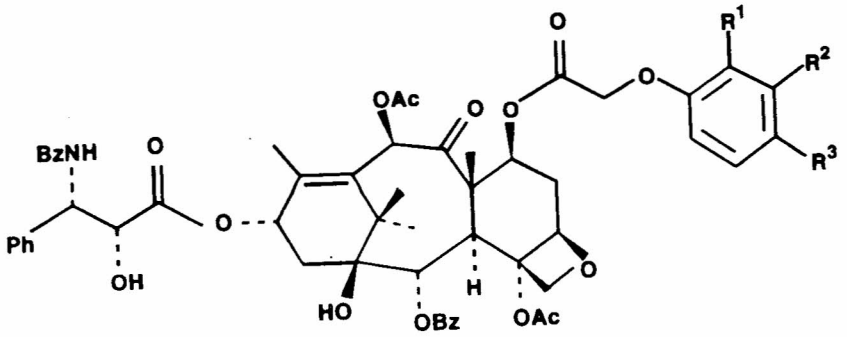
The taxol derivative **84** with a contracted A ring has been prepared by treating taxol with mesyl cloride[43]. It showed comparable activity to taxol in a tubulin disassembly assay, but did not show significant cytotoxicity against KB cells in a cell culture assay.

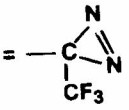
Reduction of 11,12 double bound of 10-DAB **20** leads to a dihydro derivative which was found to be less active than 10-DAB and taxol in microtubule assembly assay[55] Thus, the 11, 12 double bond is essential for activity.

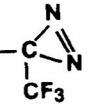
Photoaffinity Analogues

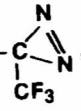
The molecular mechanism(s) through which taxol exerts its antitumour effect, both *in vivo* and *in vitro* has been extensively studied during the last decade. Taxol is a potent inhibitor of cell replication that blocks cells in the mitotic phase of the cell cycle. It interferes with the normal function of microtubule, but unlike other antimitotic agents of natural origin such as colchicine, podophyllotoxin and vinca alkaloids that inhibit microtubule assembly, taxol promotes the polymerisation of stable microtubules. This action of taxol renders microtubules resistant to depolymerisation and inhibits their normal functions. To understand the interaction between taxol and microtubule, a good comprehension of the binding site(s) for taxol on the microtubule is essential. Photoaffinity analogues of taxol are used as investigational tools to unravel the binding sites on microtubules. Such studies also help in the design of new drugs and analogues with taxol like activity.

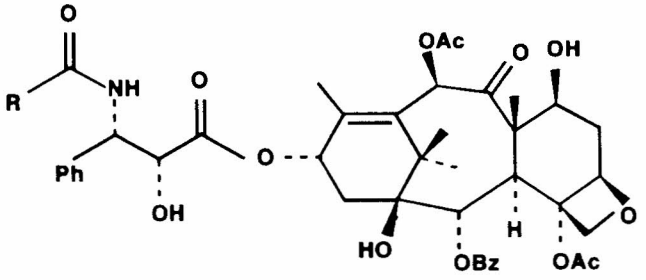
Photoaffinity labels at 7-position of taxol were studied by Kingston *et al*[56]. Out of the analogues the compounds **85** to **88** could be prepared in the radiolabelled forms. The tritiated version of the compound appeared to be highly reactive with tubulin. Carboni *et al*[57] have described the synthesis of a photoaffinity analogue **89** of taxol with 7-hydroxyl group esterified with 5-azido-2-nitrobenzoic acid. It retained taxol like activity. Another azide analogue. *N*-([3,5-^{3}H]-4-azidobenzoyl)-*N*-debenzoyltaxol **90** binds primarily to β-subunit, only 20% of the incorporated label was found in α-subunit[58].



86 $R^1 = NO_2$, $R^2 = H$, $R^3 =$ 

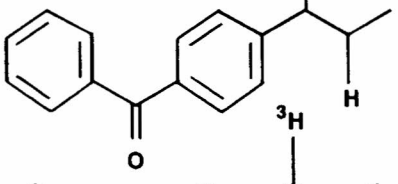
87 $R^1 = H$, $R^2 = H$, $R^3 =$ 

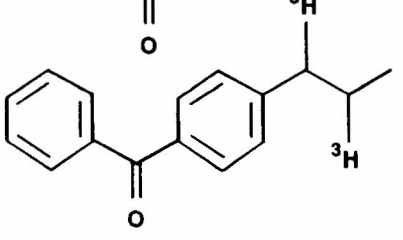
88 $R^1 = H$, $R^2 =$  , $R^3 = H$

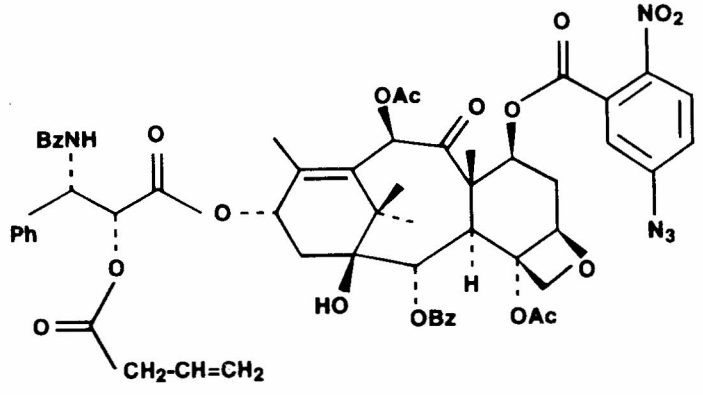


90 R = 4-(N_3)-C_6H_4

91 R = 4-(PhCO)-C_6H_4

92 R = 

93 R = 



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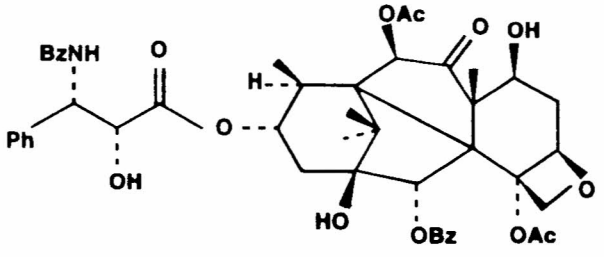

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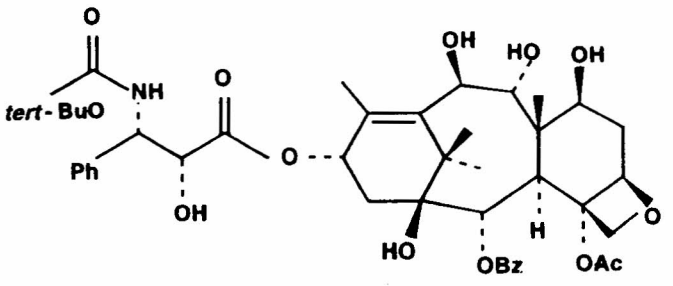

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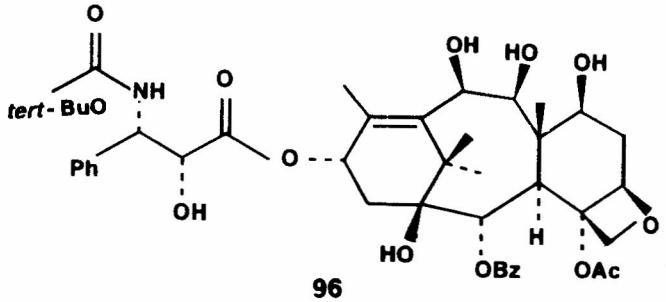

96

The azide analogue **90** exhibited better microtubule assembly activity, greater cytotoxicity towards J774.2 cells, and more specific and efficient photolabelling of the β- subunit of tubulin than the analogue **91** bearing benzophenone- related photoreactive moiety[59]. Recently, 3′-*N*-3- (4-benzoylphenyl)propanoyl-3′-*N*- debenzoyltaxol **92** and its ditritiated derivative **93** have been prepared and evaluated for their ability to photolabel tubulin and *P*-glycoprotein[60].

Photochemical and Electrochemical Modifications of Taxol and Taxotere

Promoted by the reports that taxol can function as a direct photoaffinity labeling agent towards tubulin, Chen *et al*[61] examined the photochemistry of taxol. When taxol was irradiated with 254 nm NV light, a novel pentacyclic taxol isomer **94** was obtained which contained a new bond between C-3 and C-11.

Following the successful preparation[62] of 9α- dihydrotaxol by partial synthesis from 13-acetyl-9α-dihydrobaccatin III isolated from *Taxus canadensis*, and the former analogue proving highly cytotoxic *in vitro*. Pulicani *et al*[63] reported the preparation of 9-dihydro-10-deoxy- and 10- deacetoxy-taxoids by electrochemical reduction. Taxotere on electrochemical reduction in methanol in the presence of ammonium chloride gave 9α- dihydrotaxotere **95** and 9β- dihydrotaxotere **96**. Under the same conditions, the electrochemical reduction of taxol gave 10-deacetoxytaxol. Calcium chloride as well as magnesium and cerium chlorides and to some extent strontium and lithium chloride favour 10- dehydroxylation in the taxotere series. All these taxotere analogues retained the biological activity.

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