



Invited review

## Rational approaches, design strategies, structure activity relationship and mechanistic insights for anticancer hybrids



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### ABSTRACT

A Hybrid drug which comprises the incorporation of two drug pharmacophores in one single molecule are basically designed to interact with multiple targets or to amplify its effect through action on another bio target as one single molecule or to counterbalance the known side effects associated with the other hybrid part. The present review article offers a detailed account of the design strategies employed for the synthesis of anticancer agents via molecular hybridization techniques. Over the years, the researchers have employed this technique to discover some promising chemical architectures displaying significant anticancer profiles. Molecular hybridization as a tool has been particularly utilized for targeting tubulin protein as exemplified through the number of research papers. The microtubule inhibitors such as taxol, colchicine, chalcones, combretastatin, phenstatins and vinca alkaloids have been utilized as one of the functionality of the hybrids and promising results have been obtained in most of the cases with some of the tubulin based hybrids exhibiting anticancer activity at nanomolar level. Linkage with steroids as biological carrier vector for anticancer drugs and the inclusion of pyrrolo [2,1-c] [1,4]benzodiazepines (PBDs), a family of DNA interactive antitumor antibiotics derived from Streptomyces species in hybrid structure based drug design has also emerged as a potential strategy. Various heteroaryl based hybrids in particular isatin and coumarins have also been designed and reported to possess' remarkable inhibitory potential. Apart from presenting the design strategies, the article also highlights the structure activity relationship along with mechanistic insights revealed during the biological evaluation of the hybrids.

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### 1. Introduction

Cancer, the uncontrolled, rapid and pathological proliferation of abnormal cells, is one of the most formidable afflictions in the world [1,2]. Over the years, the design of cancer chemotherapy has become increasingly sophisticated. Yet there is no cancer treatment that is 100% effective against disseminated cancer. At present cancer therapy interfering with a single biological molecule or pathway has been successfully utilized [3]. Still the problem of drug resistance and a general belief that agents modulating more than one target could have superior efficacy compared to single target drugs [4,5] has led to the search for molecules modulating multiple targets. Modulating multiple targets simultaneously can be achieved either by the combination of multiple drugs with different mechanisms or by single chemical entity that could modulate

several targets of a multi-factorial disease. As a result, there is increasing interest in the discovery of agents that concomitantly address more than one biological target for cancer treatment [6,7].

Cocktail of drugs (Combination therapy), one of the strategies employed by clinicians to treat unresponsive patients [8] has further encouraged the researchers globally towards the design of ligands comprising two pharmacophores in a single biological molecule modulating multiple targets due to problems associated with the combination therapy [9]. The molecular hybridization (MH) is a strategy of rational design of such ligands or prototypes based on the recognition of pharmacophoric sub-units in the molecular structure of two or more known bioactive derivatives which, through the adequate fusion of these sub-units, lead to the design of new hybrid architectures that maintain pre-selected characteristics of the original templates [10]. It is a new concept in drug design and development to produce a new hybrid compound with improved affinity and efficacy, when compared to the parent drugs. Pharmacophore hybridization is believed to be analogous to conventional combination therapy, with the exception that the two drugs are covalently linked and available as a single

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entity (Fig. 1) [11]. The selection of the two principles in the dual drugs is usually based on their observed (or anticipated) synergistic or additive pharmacological activities to enable the identification of highly active novel chemical entities. Hybrid drugs are basically designed to counterbalance the known side effects associated with the other hybrid part or to amplify its effect through action on another bio target or to interact with multiple targets as one single molecule [12,13] lowering the risk of drug–drug interactions and minimizing the drug resistance [9].

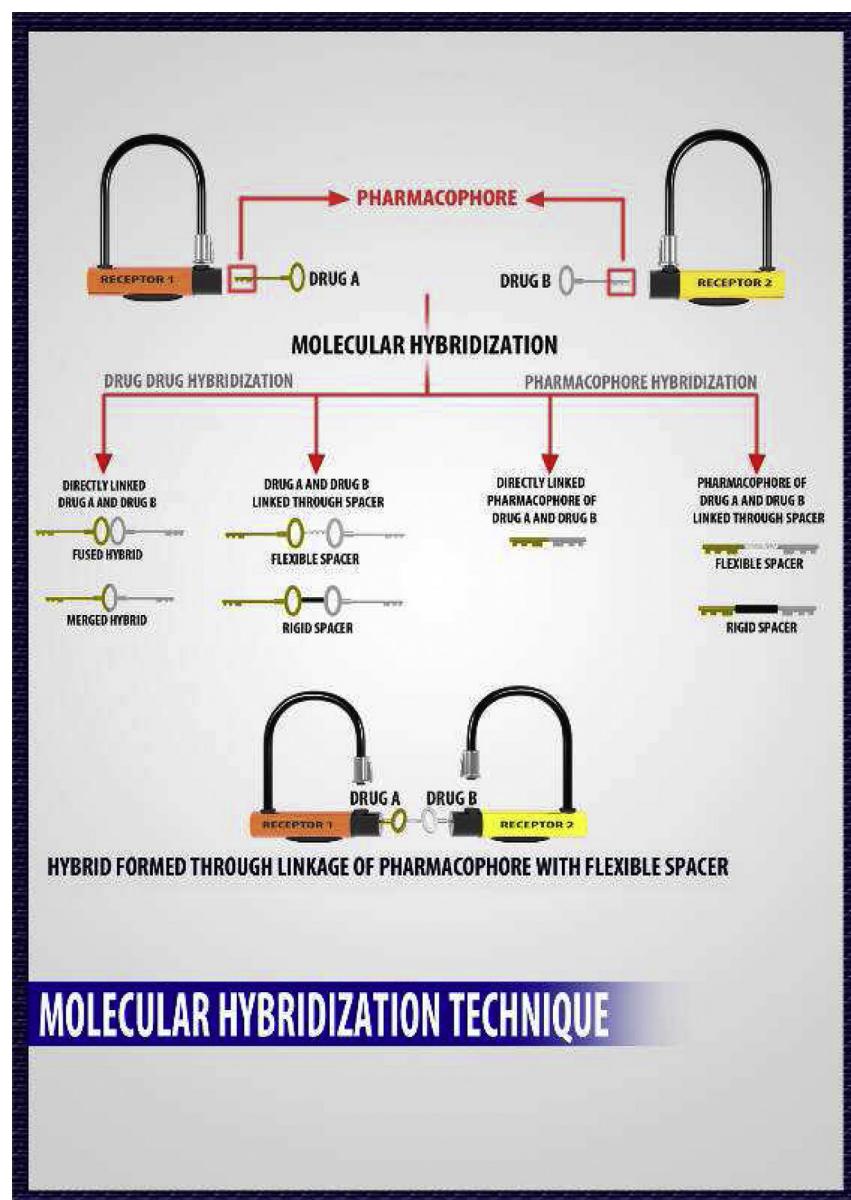
There are some reviews dealing with the concept of molecular hybridization and the promises/challenges associated with these hybrid molecules along with recent advances on anticancer hybrids. Future aspects of the hybrid drugs have also been critically discussed in the existing reviews. However this article presents some interesting strategies/rational approaches employed for the design of anticancer hybrids by eminent scientists, researchers and scholars all around the world. Apart from presenting the design strategies, the article also highlights the structure activity

relationship along with mechanistic insights revealed during the biological evaluation of the hybrids. For presenting the rational approaches, we have basically classified the strategies for hybrid structures on the basis of the one of the core functionalities of their chemical architecture. The classification is as follows:

#### Classification:

##### 1) Tubulin inhibitors based anticancer hybrids

- i) Hybrid  $\alpha$ -bromoacryloylamido chalcones
- ii) Chalcones-Imidazolones hybrids
- iii) Furofused chalcones as hybrid structures
- iv) Nitric acid donating Chalcone hybrids
- v) 1, 2, 3-Triazole tethered  $\beta$ -lactam-Chalcone bifunctional hybrids
- vi) Bifendate – Chalcone Hybrids
- vii) Triazole tethered pyrazolyl chalcones-nitro benzyl hybrids
- viii) Combretastatin A4 – Steroid hybrid



**Fig. 1.** Molecular hybridization.

- ix) Lamellarin D-Combretastatin A-4
- x) Combretastatin A-4/lamellarin T hybrids
- xi) Combretastatin-amidobenzothiazole conjugates
- xii) Combretastatin-isocombretastatin Hybrids
- xiii) Chromone-based analogues of combretastatins
- xiv) 2,3-dihydroquinazolinone-cis restricted combretastatin hybrids
- xvi) Colchicine-Caulerpenyne hybrids
- xvii) Bivalent colchicines-tubulinizine hybrids
- xviii) Tubulin-directed DO3A – colchicines conjugate
- xix) Tubulin Ligands with adamantane core
- xx) “Combretatropones” – hybrids of combretastatin and colchicines
- xxi) Thiocolchicine – podophyllotoxin conjugates
- xxii) Colchicine-SAHA hybrids
- xxiii) Colchicine-Adamantane Conjugates
- xxiv) Bisepipodophyllotoxins Hybrids
- xxv) Lignopurines: Hybrids of cyclolignans and purines
- xxvi) Acrylamidopodophyllotoxin conjugates
- xxvii) 4 $\beta$ -alkylamidochalcone and 4 $\beta$ -cinnamido linked podophyllotoxins
- xxviii) Paclitaxel-chlorambucil hybrids
- xxix) Discodermolide-paclitaxel hybrids
- xxx) Vinca- Phomopsin hybrids
- xxxi) Vindoline – Thiocolchicine hybrid.
- 2) Isatin based anticancer hybrids
  - i) Uracil-isatin conjugates
  - ii) Triazole tethered isatin conjugates
  - iii) Isatin – Benzothiazole Analogs
  - iv) Isatin-4-pirazinylquinoline hybrids
  - v) Isatin-Thiazolidinone Hybrid
- 3) Coumarin based anticancer hybrids
  - i) Coumarin-pyrazoline hybrids
  - ii) Coumarin-stilbene hybrid compounds
  - iii) Coumarin-benzimidazole hybrids
  - iv) Coumarin – chalcone hybrid
  - v) Coumarin-Manosterol Hybrids
- 4) Steroidal anticancer hybrids
  - i) Estradiol-chlorambucil hybrids
  - ii) Geldanamycin-estradiol hybrid
  - iii) Geldanamycin-testerone hybrid
  - iv) Isothiocyanate-progesterone hybrids
  - v) Hybrid aza-steroid alkylators
  - vi) Platinum based steroidal hybrids
  - vii) Estradiol-PEG-linked platinum(II)hybrid molecules
  - viii) Imidazole derived steroidal hybrids
- 5) Pyrrolo benzodiazepine (PBD) based hybrids
  - i) PBD Hybrids with Polyaromatic planar ring systems
  - ii) Benzothiazoles and pyrrolo [2,1-c] [1,4] benzodiazepin-5-one
  - iii) Bisindole linked pyrrolo [2,1-c] [1,4]benzodiazepine conjugates
  - iv) PBD-indole conjugates
  - v) Anthranilamide-PBD Conjugates
  - vi) Naphthalimide – PBD Hybrids
  - vii) 2,5-diaryloxadiazole – pyrrolobenzodiazepine
- 6) Non classified hybrids
  - i) psorospermin – quinbenzoxine hybrids
  - ii) Norindenoisoquinoline-Camptothecin Hybrids
  - iii) Piperazinyl benzothiazole/benzoxazole-1,3,4-oxadiazole-2-thiol hybrids
  - iv) Tyrosine – Chlorambucil hybrids
  - v) Platinum – Acridine Hybrids
  - vi) Novel Arylsulfonylilide-Oxindole Hybrids
  - vii) Indole-barbituric acid hybrids
  - viii) Tyrosine – nitrogen hybrids
  - ix) Benzo [4,5]imidazo[1,2-d] [1,2,4]thiadiazole –  $\alpha$ -bromoacryloyl hybrids
  - x) 2-phenylbenzofuran-imidazole hybrids
  - xi) Imidazole scaffold-based 2-benzylbenzofuran
  - xii) 1-deoxyojirimycin-aryl-1,2,3-triazoles hybrids as angiogenesis inhibitors
  - xiii) Novel furozan-based nitric oxide-releasing derivatives of Oridonin
  - xiv) Isoflavene-propranolol hybrids
  - xv) Dithiocarbamates – triazole hybrids
  - xvi) 1,2,3-triazole-dithiocarbamate-urea hybrids
  - xvii) Tetrahydro- $\beta$ -carboline-1,3,5-triazine hybrids
  - xviii) Hybrid G – quadruplex ligands
  - xix) D- and L-tyrosine-chlorambucil analogs
  - xx) Indole, pyrazole, chromone and pyrimidine based conjugates
  - xxi)  $\alpha$ -bromoacryloylamido-5-benzylidene thiazolidine-2,4-dione
  - xxii) Isoxazole-benzoquinone hybrids
  - xxiii) Quinoxaline – carbohydrate hybrids
  - xxiv) Hybrid acetogenins
  - xxv) Platinum-acridine hybrid agents
  - xxvi) NSAID Based Hybrids.

## 2. Design strategies/rational approaches

### 2.1. Tubulin inhibitors based hybrids

Microtubules are extremely important in the process of mitosis, during which the duplicated chromosomes of a cell separated into two identical sets before cleavage of the cell into two daughter cells. Their importance in mitosis and cell division makes them an important target for anticancer drugs. Microtubules seems to be the favorite target of naturally occurring, presumably self-protective, toxic molecules that are produced by a large number of plants and animals, ranging from algae to sea hares and most microtubule- targeted compounds have been discovered in large-scale screens of natural products [14–16]. The dynamic process of microtubule assembly and disassembly can be blocked by various agents that bind to distinct sites in the  $\beta$ -tubulin subunit. By interfering with microtubule function *in vitro*, these agents arrest cells in mitosis, eventually leading to cell death, by both apoptosis and necrosis. So far, three binding domains have been identified [17]: a) Colchicine site close to the  $\alpha/\beta$  interface – Colchicine binds to a site near the intra-dimer interface and alters lateral contacts within the microtubule, blocking microtubule polymerization [18]. Agents that bind in the colchicine-binding site of tubulin and inhibit cancer cell proliferation include phenstatin (1), combretastatin A-4 (2), colchicines (3), steganacin (4), podophyllotoxin (5) and certain other synthetic analogs of these compounds. b) Area where the vinca alkaloids bind – Vinca alkaloids inhibit microtubule assembly by cross-linking at the inter-dimer interface; they sterically distort the protofilament and induce tubulin to form alternate spiral polymers [19,20]. c) Taxane-binding pocket - The mechanism of action of taxanes is quite different from that of the other two, for it promotes the assembly of microtubules, resulting in highly stable, nonfunctional polymers [21]. Taxanes bind at the M loop on the  $\beta$ -subunit, stabilizing lateral contacts between protofilaments (Fig. 2) [22–25]. The success of Tubulin inhibitors as single entities has further tempted the researchers to design hybrid structures comprising these agents as one of the functionality of the planned conjugates. Literature survey reveals that among the Tubulin inhibitors, colchicines, chalcones, combretastatins, vinca alkaloids

and paclitaxel based hybrids have been designed and most of the hybrids have displayed significant anticancer potential.

### 2.1.1. Chalcone based hybrids

The chalcones (Fig. 2) are a series of biaryl propenones, which show potent toxicity to several cancer cell lines and interact with tubulin at its colchicines binding site [26–30]. The most potent agents are those possessing a trimethoxy unit on one aryl ring and a 3-hydroxy-4-methoxy phenyl ring as the other aryl ring [31–35]. During the last decade, several chalcone analogs and derivatives have been designed with the enone moiety replaced by a heterocyclic ring in order to get rigid analogs.

**2.1.1.1. Hybrid  $\alpha$ -bromoacryloylamido chalcones** [36]. The reactivity of  $\alpha$ -bromoacryloyl moiety (present in cytotoxic alkaloids Discorhabdin A [37], Discorhabdin G [38] and distamycin like minor groove binders such as PNU-166196) [39]) has been hypothesized to be based on a first-step Michael-type nucleophilic attack, followed by a further reaction of the former vinylic bromo substituent  $\alpha$  to the carbonyl, leading successively to a second nucleophilic substitution [40]. Reports indicating that the  $\alpha$ ,  $\beta$ -unsaturated ketone system of chalcones acts as a Michael acceptor and alkylation at the  $\beta$ -position of the enone system by biological nucleophiles may be one of the mechanism for their antiproliferative activity led to the design of two novel and unusual classes of hybrid  $\alpha$ -bromoacryloylamido chalcones containing a pair of Michael acceptors (Fig. 3) [41], in view of their cellular nucleophilic trapping abilities. The hybrids were evaluated for antiproliferative activity against five cancer cell lines. Compounds 2–4 were found to be the most active (more potent than amino chalcones) with an IC<sub>50</sub> value range of 0.24–0.75  $\mu$ M, 0.25–0.73  $\mu$ M, 0.51–0.84  $\mu$ M against the growth of murine leukemia (L1210), murine mammary carcinoma (FM3A), human T-lymphoblastoid (Molt/4 and CEM) and human cervix carcinoma (HeLa) cells. Flow cytometry with K562 cells showed that the most active compounds resulted in a large proportion of the cells entering in the apoptotic sub-G0–G1 peak. Moreover, compound 2 induced apoptosis through the mitochondrial pathway and activated caspase-3.

**2.1.1.2. Chalcones-imidazolones hybrids** [42]. Medicinal attributes of imidazolones have been well reported [43]. The apoptosis inducing and Hdm 2 E3 ligase inhibiting ability of this class led to the design of chalcone linked imidazolones (Fig. 4) [44]. The molecules were evaluated for their anti-cancer activity against a panel of 53 human tumor cell lines derived from nine different cancer types: leukemia, lung, colon, CNS, melanoma, ovarian, renal, prostate and breast. Compound 5, 6 displayed good anti-cancer activity with GI<sub>50</sub> values ranging from 1.26 to 13.9  $\mu$ M. With compound 5 and 6, cell cycle arrest was observed in G2/M phase.

**2.1.1.3. Furofused chalcones as hybrid structures** [45]. Promising cytotoxicity profile of previously reported hybrid chalcones, enhanced activity with structurally modified chalcone templates [46,47], chemo preventive and cytotoxic effects of furo

fused chalcones [48] and significant anticancer potential with the placement of pyrazole ring as Ring B of chalcones [49] collectively motivated the authors to design a new class of chalcones with dihydrobenzofuran moiety as A-ring and substituted phenyl or pyrazole moiety as B-ring (Fig. 5). The hybrids were tested for their cytotoxic activity against PC-3 (prostate cancer), HT-29 (colon cancer), B-16 (mouse macrophages) and NCI-H460 (lung cancer) cell lines. Compounds 7, 8 and 9 (IC<sub>50</sub> = 8.4, 7.9 & 5.9  $\mu$ M) showed significant activity against PC-3 cell line.

**2.1.1.4. Nitric oxide donating chalcone hybrids** [50]. Numerous reports on the mediation of cytotoxic effects of metabolic NO release [51–54] such as (i) prevention of metastasis by NO assisting macrophage to kill tumor cells [55] ii) significant potential of NO-NSAID derivatives such as NCX4040 and ketoprofen-NO hybrids towards the growth inhibition of cancer cells [56] (iii) revelations that COX-2 pathway alone did not seem sufficient to inhibit cell proliferation and NO release strongly contributes to this activity [57] prompted the authors to link nitric oxide donating moiety with chalcone resulting in the formation of a compact scaffold speculating synergism to result in significant anticancer effect (Fig. 6). Thus nitric oxide (NO) donating chalcone hybrids were synthesised by binding amino chalcones with different NO-donating moieties including; nitrate esters, oximes and furoxans. These derivatives were tested for anticancer activity against various cancer cell lines. The hybrids 10 and 11 exhibited remarkable activity against different types of cancer cell lines especially against the colon and melanoma cancer cell lines. The nitrate moderate selectivity was exhibited by 11 towards colon cancer cell lines.

**2.1.1.5. 1,2,3-Triazole tethered  $\beta$ -lactam-Chalcone bifunctional hybrids** [58]. Reports on antitumor potential of  $\beta$ -lactams against a number of human cancer and normal cell lines, in particular 1,4-diaryl-2-azetidinones [59] exhibiting anti-proliferative activity against the MCF-7 and MDA-MB-231 human breast carcinoma cell lines through inhibition of tubulin polymerisation and subsequent G2/M arrest of the cell cycle [60] along with certain properties of triazole like moderate dipole character, hydrogen bonding capability, rigidity and stability under *in vivo* conditions in addition to their anticancer activity [61] led to the design of triazole tethered  $\beta$ -lactam-Chalcone bifunctional hybrids (Fig. 7). The synthesized  $\beta$ -lactam-chalcone hybrids were evaluated for their anticancer activity against four human cancer cell lines viz.A-549(lung), PC-3 (prostate), THP-1(leukemia) and Caco-2 (colon) using sulforhodamine B assay. The most potent compound exhibited an IC<sub>50</sub> value of <1, 67.1, <1 and 6.37  $\mu$ M against A-549(lung), PC-3(prostate), THP-1(leukemia), and Caco-2(colon) cell lines.

**2.1.1.6. Bifendate – Chalcone hybrids** [62]. Over expression of P-glycoprotein has been identified as one of the major problems to successful cancer chemotherapy. It has also been reported to be one of the mechanisms underlying multidrug resistance [63]. Revelations from literature survey regarding inhibitory effect of chalcones on P-Glycoprotein [64,65] and success of Bifendate derivatives in reversing P-glycoprotein mediated multidrug resistance [66] led to the design of Bifendate–chalcone hybrids (Fig. 8) in view of speculated enhanced inhibitory effect on P-Glycoprotein. Most of the target compounds exhibited strong P-glycoprotein inhibitory effect than the lead compound bifendate. Compounds 14, 15 and 16 more potently reversed P-glycoprotein mediated multidrug resistance than verapamil through blocking the drug efflux function of P-gp. Detailed investigation showed that 16 did not inhibit expression of P-glycoprotein at mRNA and protein levels. Additionally, the chemo-sensitizing effect of 16 persisted much longer (>24 h) than

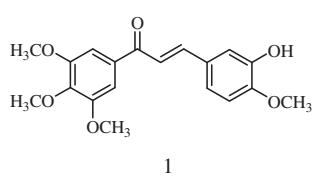
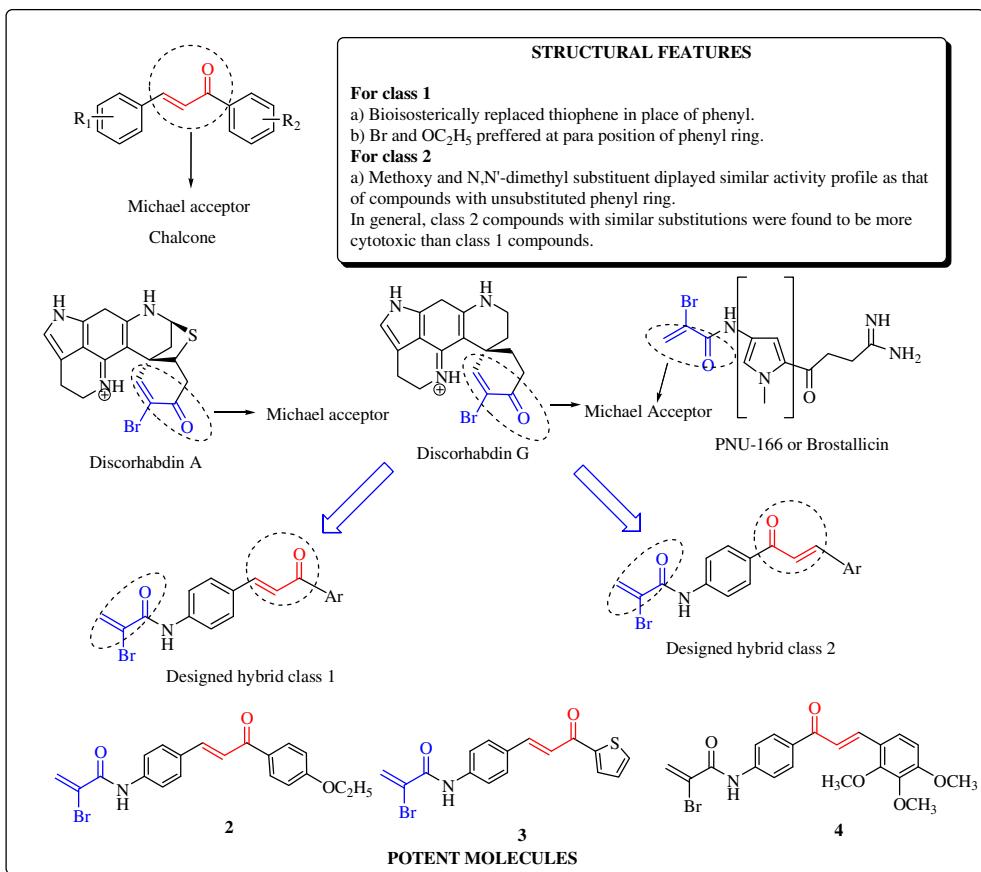


Fig. 2. Structure of most potent chalcone

Fig. 3. Hybrid  $\alpha$ -bromoacryloylamido chalcones.

that of verapamil (<6 h). Compound 16 showed no stimulation of the P-glycoprotein ATPase activity, suggesting it was not a P-glycoprotein substrate. Besides, the intrinsic cytotoxicity of 16 was very low ( $IC_{50} > 200 \mu M$ ) *in vitro*, 16 represents a promising lead to develop P-gp-mediated MDR reversal agents in cancer chemotherapy.

**2.1.1.7. Triazole tethered pyrazolyl chalcones-nitro benzyl hybrids [67].** Significant anticancer potential of rigid combretastatins/chalcones [68], triazoles [69–71] and nitroarenes [72] as per earlier reports encouraged the research group lead by Jagjeet *et al.* to design molecular hybrids of pyrazolyl chalcones and p-nitro benzyl functionalities tethered by triazole ring (Fig. 9). The designed

molecules were evaluated for cytotoxic studies against three human cancer cell lines (THP, COLO-205, A-549). The results of the preliminary investigation exhibited marked dependence of the cytotoxic activity on the electronic factors with compound 17, 18 and 19 displaying moderate to significant concentration dependent % age inhibition against A-549 (85 and 95%) THP (43 and 72%). COLO-205 (99 and 72%) Placement of naphthyl and trimethoxy phenyl ring (JGPT-6) as ring A proved to be extremely beneficial in enhancing the cytotoxic potential.

### 2.1.2. Combretastatins based hybrids

Combretastatin first isolated from the bark of the South African willow tree *Combretum caffrum* is a potent tubulin inhibitor. CA-4 appears to be the most powerful antimitotic agent of this series and is remarkably simple in its chemical structure [73]. CA-4 significant cytotoxic potential against a panel of tumor cell lines [74,75] including MDR cells [76]. *In vivo*, CA-4 displayed low or no antitumor activity [77] mainly because of low water solubility, and therefore a disodium phosphate prodrug, CA-4P was introduced [78]. Due to the significant potential displayed by CA-4, several synthetic analogs of CA-4 were developed and structure–activity relationship [79–81] was established as shown in Fig. 10.

**2.1.2.1. Combretastatin A4 – steroid hybrid [82].** Breast cancer is the leading cause of cancer deaths among women worldwide and second major cause of deaths after cardiovascular disease which clearly indicates the need for effective strategies for the prevention of the disease [83]. Parihar *et al.* synthesised combretastatin A4 (CA4) analogues on steroid framework in view of anticipated anti-

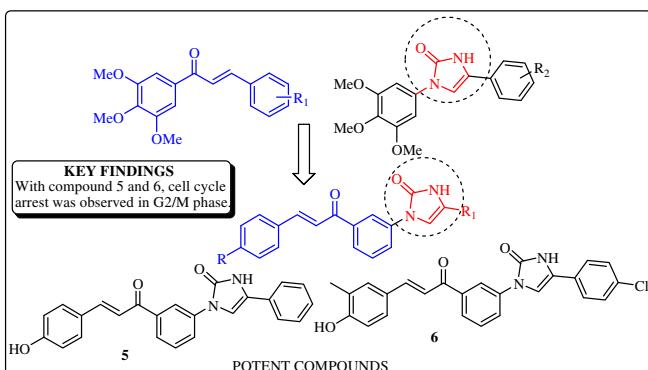


Fig. 4. Chalcones-imidazolones hybrids.

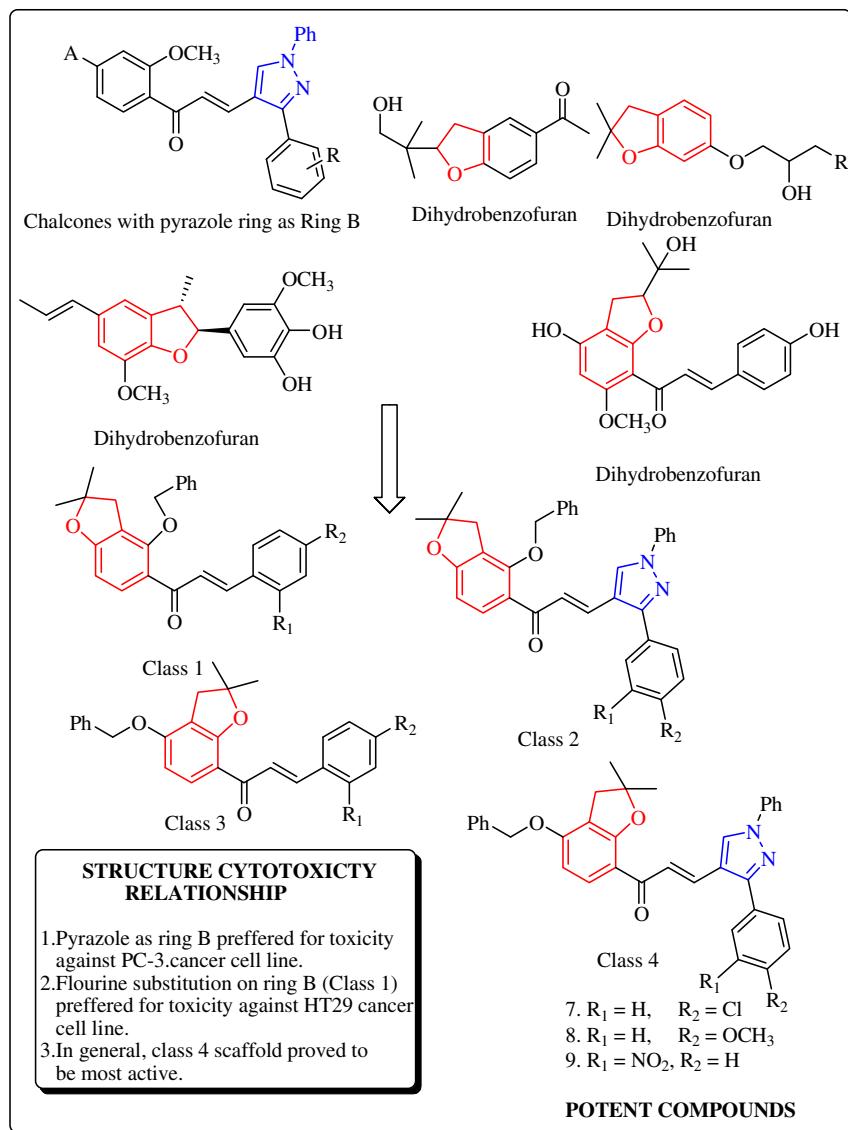


Fig. 5. Furofused chalcones as hybrid structures.

breast cancer potential. The design strategy utilized the Ring A of Estradiol as a second aryl group of combretastatin (Fig. 11) [84–88]. The synthesised analogues were evaluated for cytotoxicity against human breast cancer cell lines (MCF-7 & MDA-MB 231). The compounds were found to possess high to moderate antiestrogenic with low estrogenic activity and exhibited significant anticancer activity against both ER positive and ER negative breast cancer cells. The most potent analogue 21 displayed an IC<sub>50</sub> value of 7.5 μM and 5.5 μM against MCF-7 and MDA-MB-231 cells and also showed potent antitubulin effect (IC<sub>50</sub> = 0.96 μM). The results of tubulin inhibition effect was rationalized by docking experiments which indicated strong binding affinity of 21 to microtubule polymerase. The docking energies of cis isomers of 21 were higher than the corresponding trans isomer. Thus, cis isomer was found to be more active than the trans isomer. Eight amino acid residues were found to be interacting with 21.

**2.1.2.2. Lamellarin D and combretastatin A-4 [89].** Lamellarin D, first isolated from marine prosobranch mollusk *lamellaria* [90], is a potent topo 1 inhibitor [91,92] and induces apoptosis through

mitochondrial pathway [93] towards a large panel of cancer cell lines [94,95]. Tubulin inhibitory potential of combretastatin is well reported. Thus Shen *et al.* in view of different mechanisms of antiproliferative action of Lamellarin D and Combretastatin A-4, designed 1,2-diphenyl -5,6-dihydropyrrolo [2,1-a]isoquinoline derivatives as hybrid molecules of the two (Fig. 12). The hybrids were designed in such a way that aryl units of the hybrids closely related to the substitution pattern of lamellarin D. With the help of 3D models it was further visualized that Ring F and A in hybrid molecule matched well with the relevant Ring A and B of combretastatin A4. The hybrids were evaluated for their growth inhibitory activity *in vitro* against five human cancer cell lines, including leukemia K-562, lung carcinoma A-549, hepatocellular carcinoma SMMC-7721, gastric carcinoma SGC-7901 and colon carcinoma HCT-116. The design strategy proved to be successful as the some of the hybrids displayed significant cytotoxicity against the cell lines employed. Hybrid 22 with isopropoxy groups at 8 and 14 positions and OH at 20 and 21 positions, exhibited the most potent activity against all the five human cancer cells with the IC<sub>50</sub> value around 10 μM.

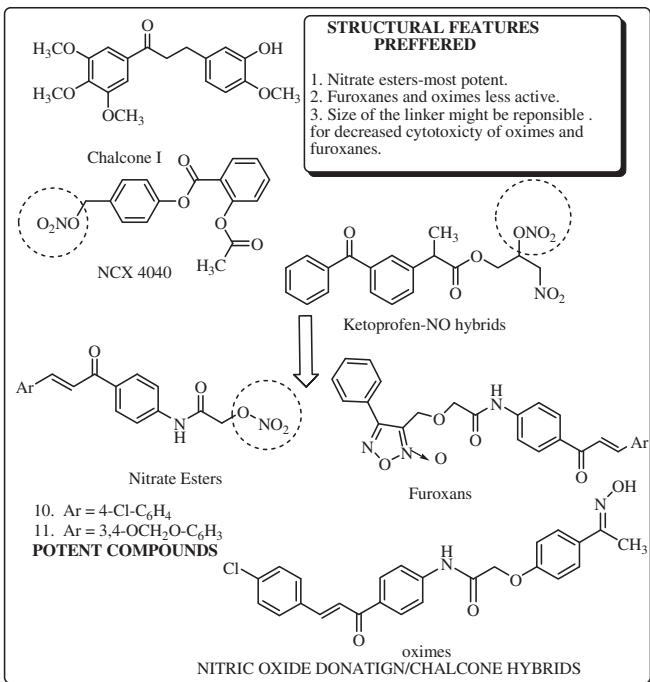


Fig. 6. Nitric acid donating chalcone hybrids.

**2.1.2.3. Combretastatin A-4-lamellarin T hybrids [96].** Lamellarin T, another secondary metabolite from the family of pyrrolic marine alkaloids displays topoisomerase I inhibitory effect, cytotoxic effects, reversion of multidrug resistance, antibacterial and antimitotic properties [97]. Lamellarin T's chemical architecture possesses a combretastatin A4-like substructure as the two aryl rings attached at the C4- and C5-positions of the pyrrole ring are rigidly maintained in a cis-relationship to one another [98]. With this background, Banwell *et al.* designed a series of 4, 5-diarylated-1H-pyrrole-2-carboxylates as hybrids of the potent antimitotic agent combretastatin A-4 and marine alkaloid lamellarin T (Fig. 13). The synthesised hybrids were evaluated for their antimitotic and cytotoxic properties. Hybrid 25 and 27, the hybrids

most closely resembling combretastatin A-4 in structure, displayed potent anti-mitotic and cytotoxic properties, owing to their binding to the colchicine bindind site on tubulin. Hybrid 25 significantly inhibited tubulin polymerization with an IC<sub>50</sub> value of 1.4 μM, Burkitt lymphoma cell growth with an IC<sub>50</sub> value of 29 nM and caused 74% inhibition of colchicine binding. Hybrid 27 significantly inhibited tubulin polymerization with an IC<sub>50</sub> value of 1.3 μM, Burkitt lymphoma cell growth with an IC<sub>50</sub> value of 31 nM and caused 74% inhibition of colchicine binding. It was observed that in the equipotent hybrids 25 and 27, each aryl unit each unit is 2-atoms away from the carbon bearing the carbomethoxy group indicating that the positioning of carbomethoxy group might be critical for activity.

#### 2.1.2.4. Combretastatin–amidobenzothiazole conjugates [99].

Mitogen-activated protein kinase (MAPKS) transduces extracellular stimuli from the cell surface to the nucleus, leading to alterations in gene expression and cell functions. Till date, three major subfamilies of MAPKS have been identified i.e. c-jun N-terminal kinases/stress-activated protein kinases (JNK/SAPks), extracellular signal-regulated kinases (ERK1/2 or p42/44 MAPK) and p38 MAPK [100]. The extracellular signal regulated kinase signaling pathway controls proliferation, differentiation and cell survival [101–103]. ERK-1/2 is primarily activated (phosphorylation) by mitogens and growth factors and plays a key role in transmission of proliferative signals in mammalian cells. Abnormal phosphorylation of ERK and MAPK occurs in cancer as well as other proliferative disorders [104]. With this background, Kamal *et al.* designed combretastatins-amidobenzothiazole hybrids (Fig. 14) in view of the reports which indicate that cytotoxicity of combretastatin A-4 is caused by affecting MAPK family of proteins and inhibitory effect on ERK phosphorylation [105] by some benzothiazole derivatives. The effect of both the functionalities on MAP kinases led to the synthesis of their conjugates. The synthesised hybrids were evaluated for anticancer activity against a panel of human cancer cell lines, effects on tubulin polymerization and ERK signaling. Compound 29 was found to be the most promising exhibiting significant cytotoxicity against MCF-7 cells (IC<sub>50</sub> = 51 nM). Significant anticancer potential of hybrid 29 was attributed to its combined effect on tubulin inhibition as well as ERK inhibition. Molecular modeling studies of hybrid 29 confirmed the binding to ERK and Tubulin.

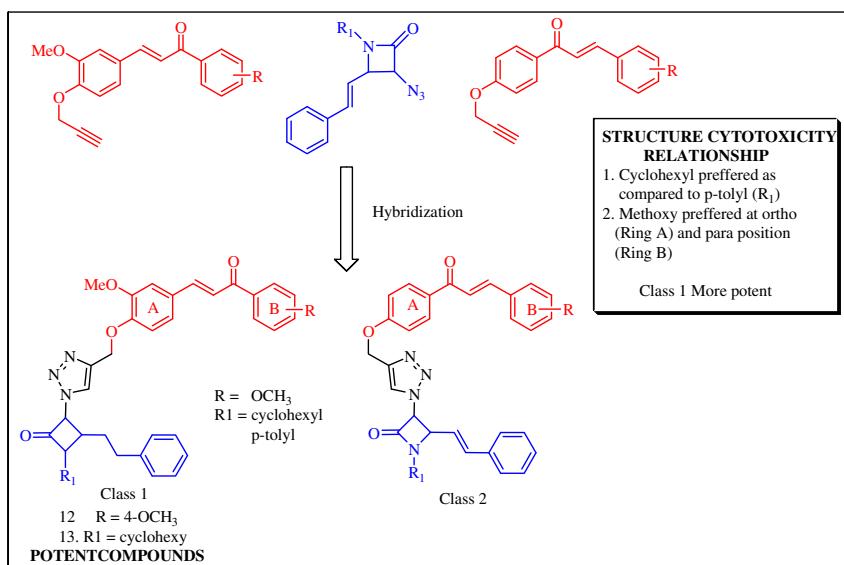
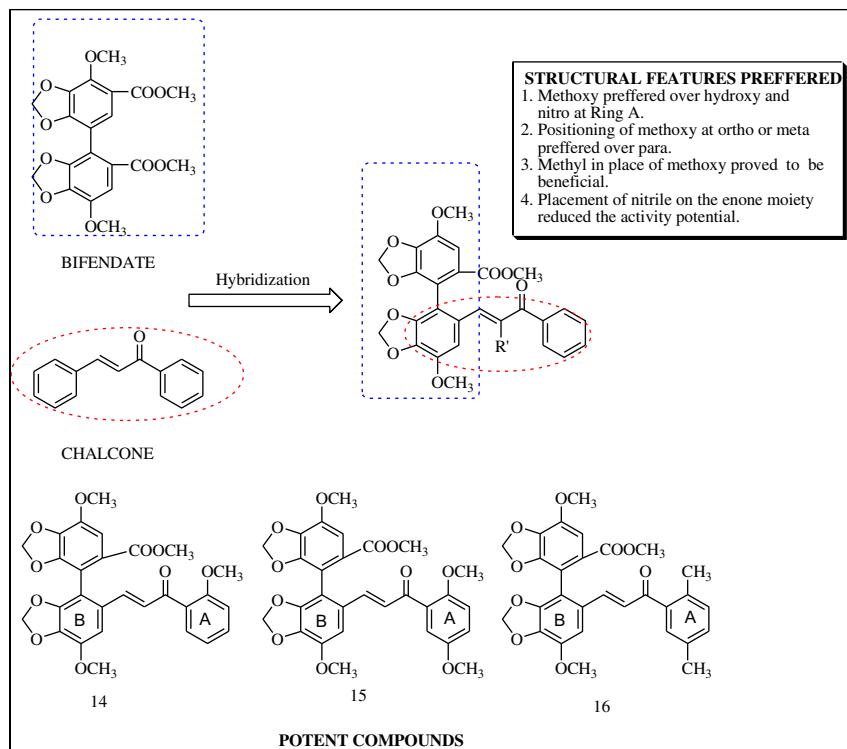
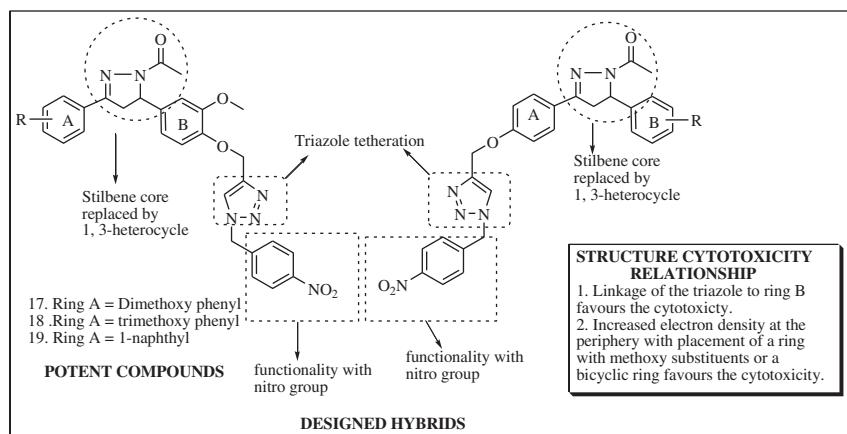
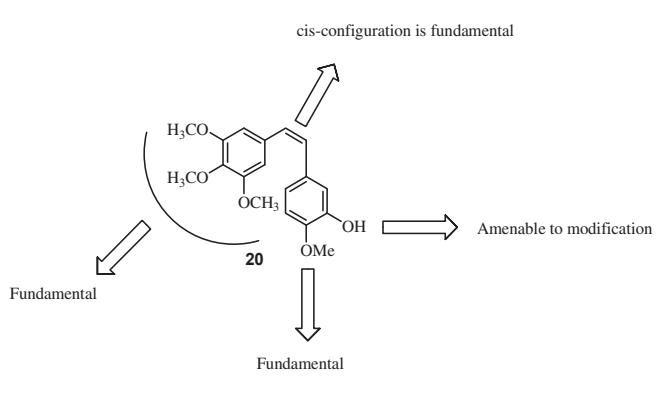


Fig. 7. 1, 2, 3-Triazole tethered β-lactam-chalcone bifunctional hybrids.

**Fig. 8.** Bifendate- chalcone hybrids.**Fig. 9.** Triazole tethered pyrazolyl chalcones-nitro benzyl hybrids.**Fig. 10.** SAR of combretastatins.

**2.1.2.5. Combretastatin-isocombretastatin hybrids [106].** The isomerization of Z-stilbene to E-isomer during storage and administration significantly reduces the inhibition of cancer cell growth and tubulin assembly [107]. This is one of the major drawbacks associated with combretastatin A-4, a potent inhibitor of tubulin assembly. Due to this, Isocombretastatin A-4 (isoCA-4), the third and “forgotten” structural isomer of the natural product gained attention during the last few years [108]. The class has striking structural resemblance to phenstatins with a 1,1-diarylethylene scaffold [109,110] and possesses biological activities comparable to that of CA-4. The ease of synthesis of this class of tubulin inhibitors, controlled geometry and promising results displayed by such compounds with modified Ring B such as apoptosis induction G2/M phase, cell cycle arrest, tubulin led to design of combretastatin-isocombretastatin hybrids, Rasolofonjatovo *et al.*

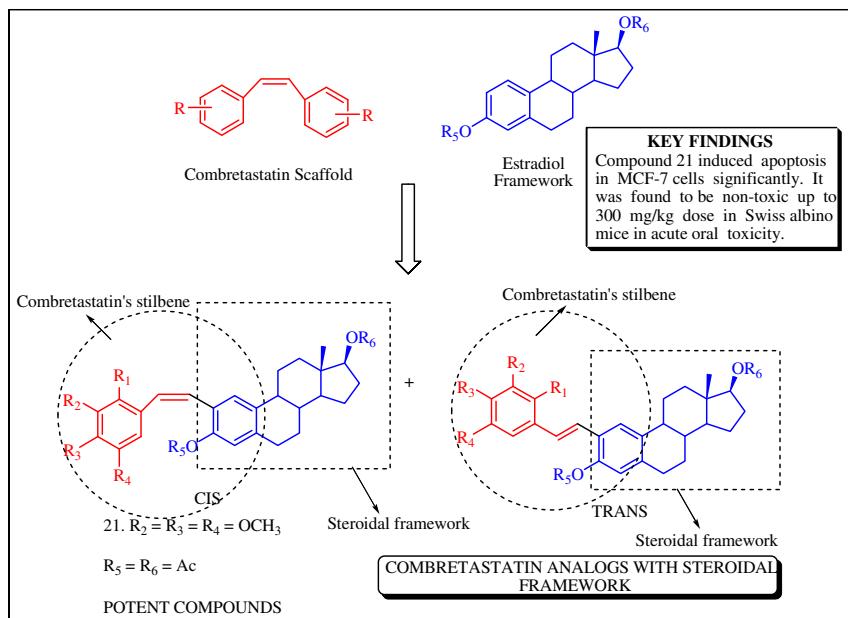


Fig. 11. Combretastatin A4 – Steroid hybrid.

synthesised a series of triarylolefins bearing the combretastatin A-4 and the isocombretastatin A-4 (Fig. 15) cores to combine the anticancer effects of CA-4 and isoCA-4 within a single structure. A three step-sequence to a regioselective hydrostannation of diary alkynes was designed to get the target compounds. The new CA-4 and isoCA-4 analogues were evaluated for their cytotoxic activity of against human colon carcinoma cell line (HCT-116) employing isoCA-4 and CA-4 as reference compounds and also for anti-tubulin activity.

**2.1.2.6. Chromone-based analogues of combretastatins as hybrid compounds [111].** Reduced cytotoxicity due to isomerization of Z-Combretastatin to E- isomer led to the design of cis-restricted analogues with an ethene bridge as part of a heterocycles [112]. Reports regarding some compounds with a bicyclic system on the bridge displaying a strong bioactivity [113] and insertion of one-carbon linker ( $C=O$ ) between the bicyclic system (indole, benzo[b]thiophene, benzo[b]furan) and the trimethoxyphenyl ring

proving beneficial for cytotoxicity as well as inhibition of Tubulin polymerization [113,114] further motivated the research group led by Quintin to synthesize new analogues of combretastatins with the ethene bridge as part of a chromone to extend the structure activity relationship (Fig. 16). These hybrids were classified according to the position of the trimethoxyphenyl ring at C-2 or C-3 of the chromone and presence or absence of a carbonyl as a linker between C-3 and the aryl ring. Most of these compounds were prepared from hesperidins or naringin, two natural and abundant Citrus flavonoids. Compound 31 was the most promising among the analogues with an  $IC_{50}/IC_{50}$  colchicine ratio of 2.4.

**2.1.2.7. 2, 3-dihydroquinazolinone-cis restricted combretastatin hybrids [115].** Quinazolinone is a naturally occurring alkaloid found in a variety of bioactive natural products and possess wide range of biological activities [116–119]. 2, 3-dihydroquinazolinones are reported to have inhibitory effects on tubulin polymerization [120,121]. In addition, their anticancer potential is well

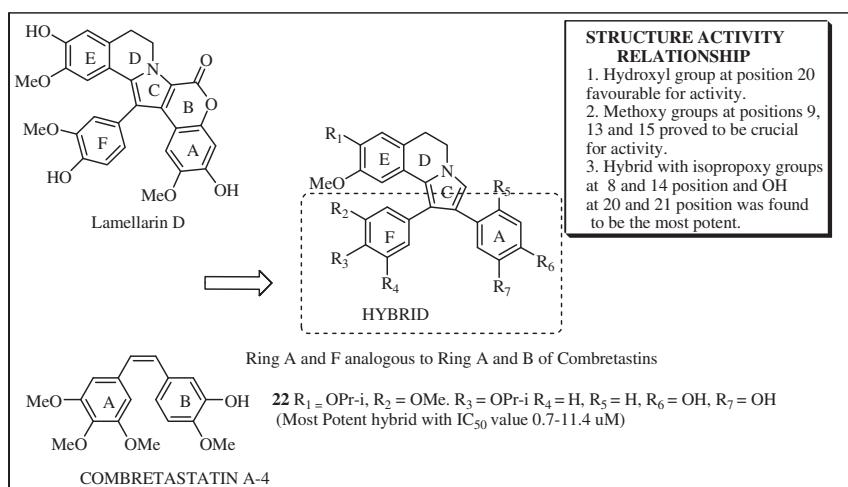
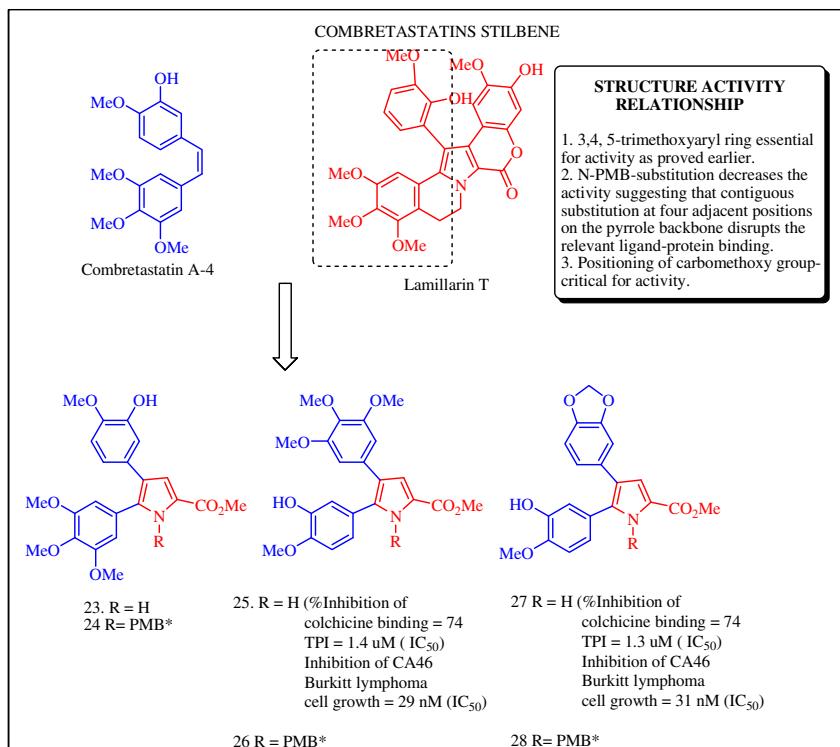


Fig. 12. Lamellarin D and combretstatin A-4.

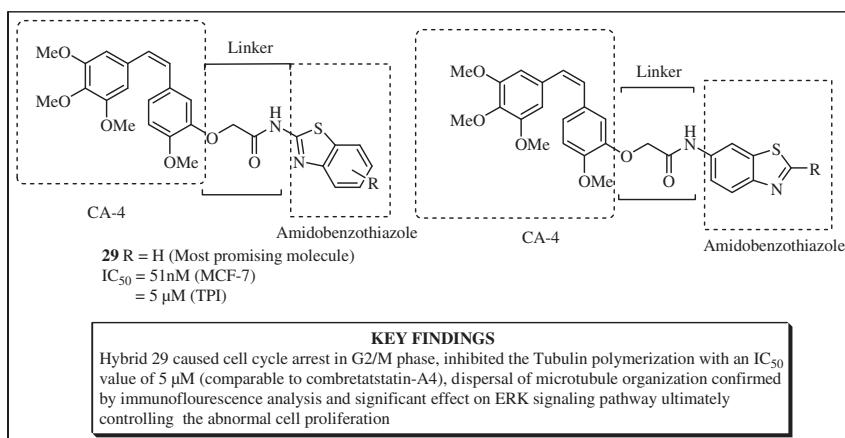


\*PMB = p-methoxy benzyl

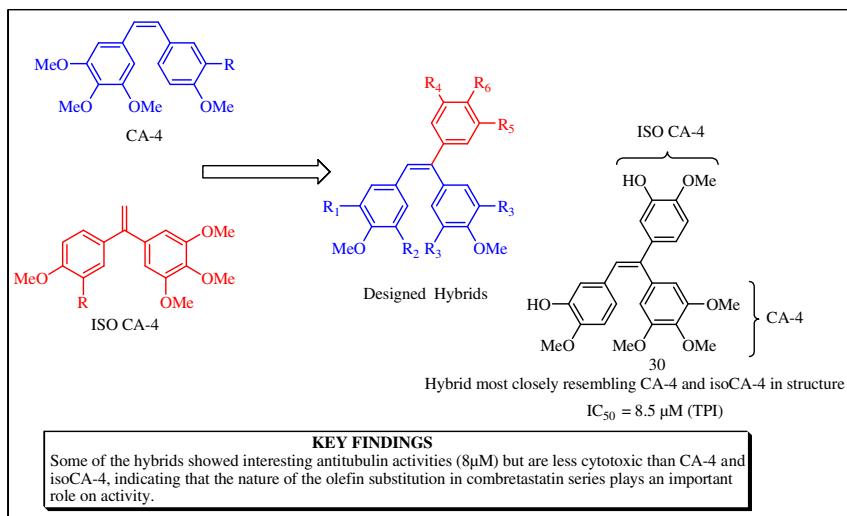
**Fig. 13.** Combtretastatin A-4/lamellarin T hybrids.

investigated and explored. On the basis of these previous reports, Kamal *et al.* designed a series of hybrids as new anticancer agents that comprises 2,3-dihydroquinazolinone and cis restricted combretastatin moieties (3,5-diaryl isoxazoline/isoxazole) (Fig. 17) with different linker architecture in view of enhancement of efficacy and to bring synergy in hybrids. Among the hybrids, compound 32 exhibited significant anticancer activity against 18 human cancer cell lines with  $GI_{50}$  values less than 1  $\mu$ M. The other compounds of the series also exhibited potent anticancer activity against MCF-7 and PC3 cancer cell lines. Hybrid 32 was found to be more effective than the conjugate partners i.e. 2, 3-dihydroquinazolinone and cis restricted combretastatin as revealed by MTT assay.

**2.1.2.8. Gallic acid based steroid phenstatin\* analogues [122].** ER- $\alpha$  serves as prognostic indicator for breast cancer [123] and is a well explored therapeutic target for the disease [124]. Tamoxifen, a selective estrogen receptor modulator is widely used for this purpose [125], however drug resistance in breast cancer [126] and the risk of endometrial cancer associated with the use of Tamoxifen has led to search of novel strategies for the targeted breast cancer [127,128]. Phenstatins as Tubulin poisons have emerged as one of the most active class acting at colchicines binding site [129] however undesired toxicity is the major concern which have been reported. Parihar *et al.* thus designed phenstatin analogues on steroid framework for selective targeting of breast cancer cells (Fig. 18). The design strategy employed phenstatin as a model



**Fig. 14.** Combtretastatin–amidobenzothiazole conjugates.



**Fig. 15.** Combretastatin-isocombretastatin hybrids.

molecule, where 3,4,5-trimethoxybenzoyl part was introduced from gallic acid and the ring A of estradiol unit was used as second aryl ring to have a phenstatin type arrangement. The hybrids were evaluated for anticancer efficacy against breast cancer cell lines i.e. MCF-7 and MDA-MB-231. The most active analogue 36 exhibited significant inhibition of MDA-MB-231 cell line with an  $IC_{50}$  value =  $5 \pm 0.03 \mu\text{M}$ , high level of inhibition of tubulin polymerization ( $IC_{50}$  value =  $0.99 \mu\text{M}$ ) and was found to be non-toxic in the Swiss albino mice up to 300 mg/kg dose. This compound also exhibited low oestrogenicity and higher anti-oestrogenicity.

### 2.1.3. Colchicine

Colchicine (Fig. 19), a natural product isolated from *Colchicum autumnale* (meadow saffron), is the classical tubulin-binding agent. It was one of the first antimitotic agents investigated. Although used in the treatment of gout, its high toxicity prevents its use in other therapies. *In vitro*, the major effect of colchicine is to cause a change in the secondary structure of tubulin by binding with a high affinity site on the heterodimer, which hinders the formation of microtubules. This binding is temperature dependent and irreversible [130]. Colchicine has also been shown to bind with a second, lower affinity site on tubulin [131]. The structure activity relationship of colchicine [132] has been summarized in Fig. 20.

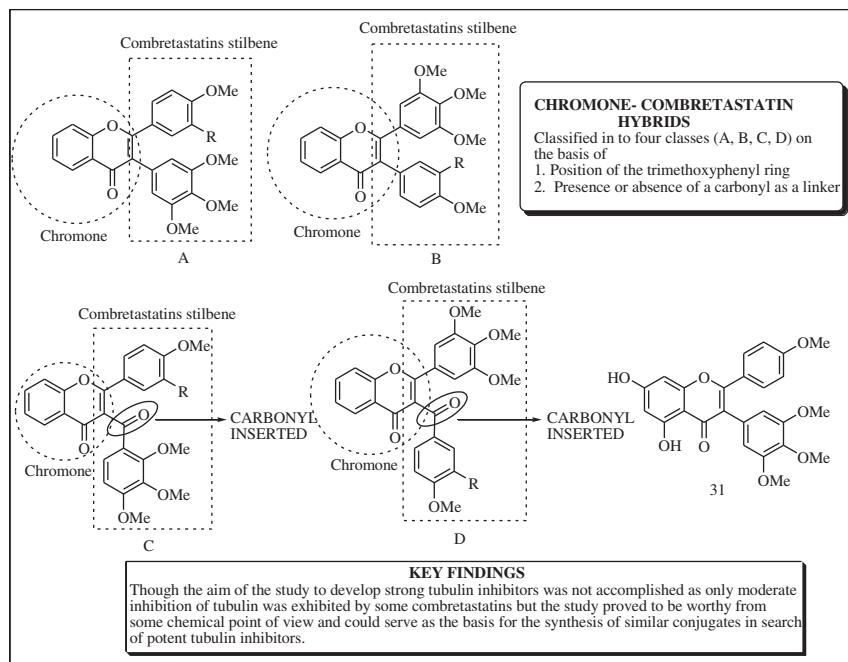
Colchicine remains to be a molecule of interest for the researchers as colchicines binding site has been most widely explored compared to the other binding sites. Despite the reports of toxicity, the molecule is still being optimized as lead for the design of new analogues and in particular has been included as core functionality for the design of several hybrid structures.

**2.1.3.1. Colchicine-Caulerpenyne hybrids [133].** Caulerpenyne (CYN) is the main toxin of *Caulerpa taxifolia* [134], tropical green seaweed and is known to inhibit the brain purified tubulin and microtubule polymerization [135]. In search of new potential molecules which can inhibit the microtubule formation process, Bourdon *et al.* designed compounds possessing the biologically active fragment of caulerpenyne (diacetoxylbutadiene moiety) and trimethoxybenzene moiety of colchicine instead of the terminal unsaturated alkyl chain of CYN (Fig. 21). Two hybrids 38 and 39 were designed and the strategy for the design of hybrid 38 was justified by its perfect superimposition with colchicine in which all heteroatoms or basic functions overlap. Assumed replacement of bis-allylic

acetate function by a thio- or amino-moiety during binding with the amino-acids of the tubulin led to the design of hybrid 39 (however extremely low yields obtained with hybrid 39 shifted the focus towards Hybrid 38 only). The hybrid exhibited weak inhibition of tubulin polymerization process, however displayed an acceptable cytotoxicity on HaCaTs cells.

**2.1.3.2. Bivalent colchicines-tubulizine hybrids [136].** Malysheva *et al.* in 2012 synthesised novel antimitotic hybrids by linking azide-containing colchicine congeners with acetylene-substituted tubulizine-type derivatives (Fig. 22), keeping in view the success with previously constructed chemical architecture of some antimitotic hybrids such as taxoid-colchicine [137], vinca alkaloids-taxoid [138] and podophyllotoxin-thicolchicine hybrids [139]. These hybrids were designed after in depth study of the colchicines and tubulizine binding site and evaluated for cytotoxicity against HBL100 epithelial cell lines along with inhibition of Tubulin polymerization. All of the tested heterodimers presented substantial cytotoxic activity ( $IC_{50} = 0.599\text{--}2.93 \mu\text{M}$ ). The hybrids were found to be less active than deacetylcolchicine, but more active compared to tubulizine. Several newly synthesized compounds exhibited substoichiometric inhibition of microtubule assembly. The highest activity among the heterodimers was achieved for ligand 40 [ $IC_{50} = 0.687 \pm 0.013 \mu\text{M}$ ,  $R = 0.71$  (half inhibitory molar ratio (ligand/tubulin) of microtubule formation *in vitro*)].

**2.1.3.3. Tubulin-directed DO3A-colchicines conjugate [140].** Theranostics (compounds with both diagnostic capability and therapeutic entity) have gained immense interest in the area of anticancer therapy [141–143] and are commonly used in the design of imaging agents in nuclear medicine to monitor the progress of therapeutic intervention. However, the use of theranostic strategies in drug discovery and innovative medicine development has prompted researchers in the magnetic resonance imaging (MRI) field to couple MR contrast agents to molecular-targeted therapeutic drugs for clinical use. Wardle *et al.* designed and synthesised novel tubulin-directed DO3A (1, 4, 7, 10-tetraazacyclododecane-N, N'', N'''-triacetic acid) – colchicine conjugate and its Gd (III) complex as drug-like MRI theranostics (Fig. 23). The tubulin-directed DO3A (1, 4, 7, 10-tetraazacyclododecane-N', N'', N'''-triacetic acid) – colchicine conjugate exhibited an efficiency similar to that of colchicine as an anti-cancer agent.



**Fig. 16.** Chromone-based analogues of combrestatins.

**2.1.3.4. Tubulin ligands with adamantine core [144].** The well established structure activity relationship of taxol reveals that the most important contribution to tubulin binding is provided by the C-13 side chain of taxol and taxotere (i.e., N-benzoyl- or N-tert-butoxycarbonyl-(2R,3S)-phenylisoseryl), while C (-OBz), C (-OAc) substituent's, and the oxetane fragment also play a role in this binding [145,146]. The main function of the taxane skeleton is to provide proper orientation of the substituent important for tubulin binding [147]. On the basis of this hypothesis, molecules possessing bicyclo [3.3.1] nonane framework (2) were synthesised by Zefirova *et al.* in 2002. However the compounds showed weak cytotoxicity and did not bind to Tubulin [148]. This weak cytotoxic profile was attributed to the conformational freedom of the bicyclo [3.3.1] nonane framework. Thus in order to get conformationally restricted analogues, analogues with adamantine core and adamantine –based taxol mimetics were synthesised (Fig. 24). The molecular modelling studies of compound A indicated that oxetane oxygen can be hydrogen bonded to the Thr 276 amino group and it corresponds exactly to the bond formed by the oxetan oxygen in taxol. Moreover, the carbonyl oxygen of structure A can be hydrogen bonded with Arg284. The synthesized adamantine-based taxol mimetics were evaluated for their *in vitro* cytotoxicity against the A549 human lung carcinoma cell line. The hybrids were found to be cytotoxic at micromolar concentrations and caused tubulin aggregation. The extent of the aggregation was maximal for N-benzoyl-(2R, 3S)-phenylisoseryloxadamantane (B). The interesting ability of structure B further led to the design of a hybrid combining adamantine-based taxol mimetic with colchicines. Biological evaluation of the hybrid 43 revealed that it possesses both microtubule depolymerizing and microtubule bundling activities in A549 human lung carcinoma cells with high cytotoxicity ( $IC_{50} = 0.0006 \mu M$ ).

**2.1.3.5. "Combretatropones"-hybrids of combretastatin and colchicines [149].** In view of the well established structure activity relationship of combretastatins and colchicine such as bis aryl system [150] (two aryls directly linked or linked via carbon bridge) with two aromatic rings [151] or an aromatic ring [152] and a tropolone

ring [153], Andres *et al.* synthesised hybrids of combretastatins and colchicines as combretatropones comprising of 1,2-diary1 ethane nucleus of combretastatin and the tropone moiety of colchicine (Fig. 25). Combretatropones 44 and 45 exhibited potent activity in the *in vitro* inhibition of tubulin isolated from bovine brain ( $IC_{50} = 8.6$  and  $12 \mu M$ ).

**2.1.3.6. Thiocolchicine–podophyllotoxin conjugates [154].** Thiocolchicine and podophyllotoxin are reported to disrupt microtubules disruption by cell cycle arrest at the G2/M phase similar to colchicines [155]. The binding to tubulin results in partial unfolding of the secondary structure of  $\beta$ -tubulin at the carboxy terminus and prevents polymerization [156,157]. With this background, Passarella *et al.* synthesised and evaluated some dimeric compounds obtained by condensation of thio-colchicine and podophyllotoxin with different dicarboxylic acids (Fig. 26). The hybrids were evaluated for cytotoxic studies against human cancer cell lines and tubulin inhibition. Immunofluorescence analysis confirmed the anti-microtubule effect in cells microtubule structure and distribution in human lung carcinoma cell line A549. In the human cell lines the  $IC_{50}$  values were in the range  $0.5\text{--}1 \mu M$ . Some conjugates exhibited marked ability to inhibit the polymerization of tubulin *in vitro* and causing significant disruption to the microtubule network *in vivo*.

**2.1.3.7. Colchicine-SAHA hybrids [158].** Histone deacetylases plays crucial roles in numerous biological processes through their repressive influence on transcription. Inhibition of histone deacetylase cause growth arrest, differentiation and apoptosis in tumor cells by inducing histone hyperacetylation and p21 expression [159–164]. A typical HDAC inhibitor consists of a capping group, a metal binding moiety and an appropriate linker. Among the several HDAC inhibitors currently in clinical trials, vorinostat (SAHA) and romidepsin (FK228) have been approved by the FDA for the treatment of cutaneous T-cell lymphoma [165–167]. Synergistic reports of antitumor effects of HDAC inhibitors with tubulin inhibitors led to the design of Colchicine-SAHA hybrids (Fig. 27) by

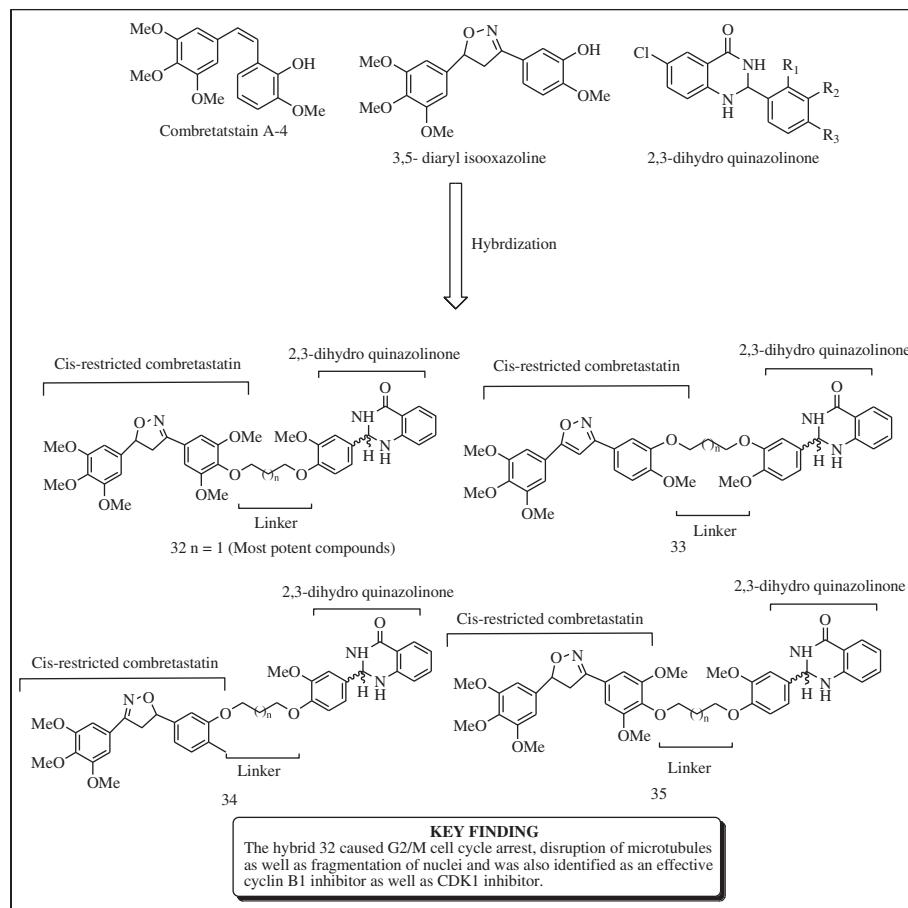
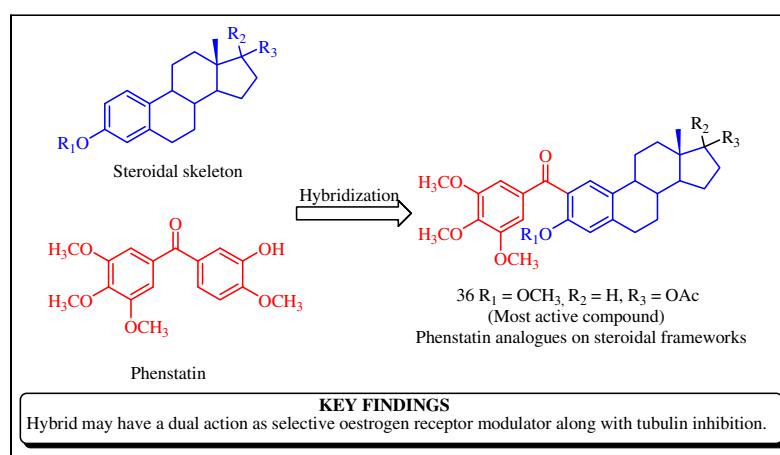


Fig. 17. 2, 3- dihydroquinazolinone-cis restricted combrestatins hybrids.

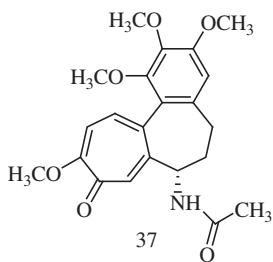
the incorporation a hydroxamic acid moiety, the key fragment of SAHA with in the tubulin inhibitors [167–170]. Zhang *et al.* synthesised dual inhibitors of tubulin, histone deacetylases and evaluated them for HDAC inhibition, *in vitro* cell cycle analysis in BEL-7402 cells as well as cytotoxicity in five cancer cell lines. Linker length was systematically varied to determine the most suitable

molecule. All the hybrids exhibited potent HDAC inhibition activity which suggested that colchicine moiety is an appropriate capping group for HDAC inhibitors. Compound 46 showed the strongest HDAC inhibitory activity [HDAC-1 ( $1.33 \pm 0.07 \mu\text{M}$ ) HDAC-3 ( $1.36 \pm 0.68 \mu\text{M}$ ) HDAC-6 ( $3.43 \pm 0.25 \mu\text{M}$ ) as well as powerful anti-proliferative activity against A431 ( $\text{IC}_{50} = 0.242 \mu\text{M}$ ), A549



\*Phenstatin based hybrid has been included in this section due to their striking structural resemblance to Isocombreastatins

Fig. 18. Gallic acid based steroid phenstatin analogues.

**Fig. 19.** Colchicine.

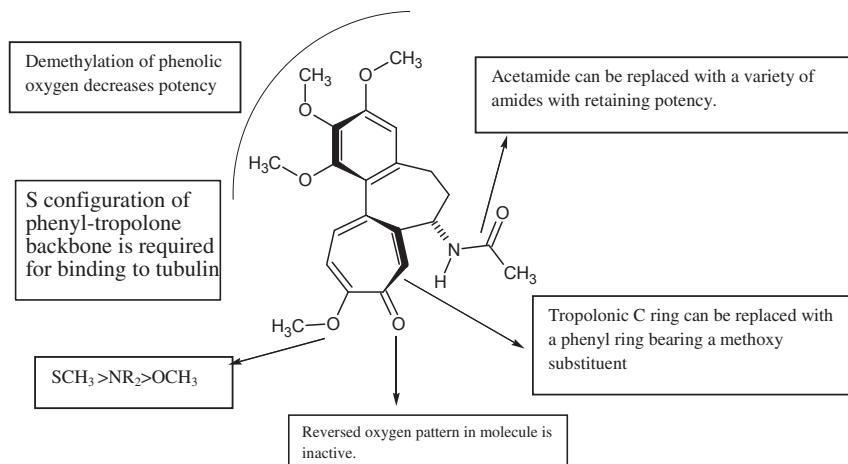
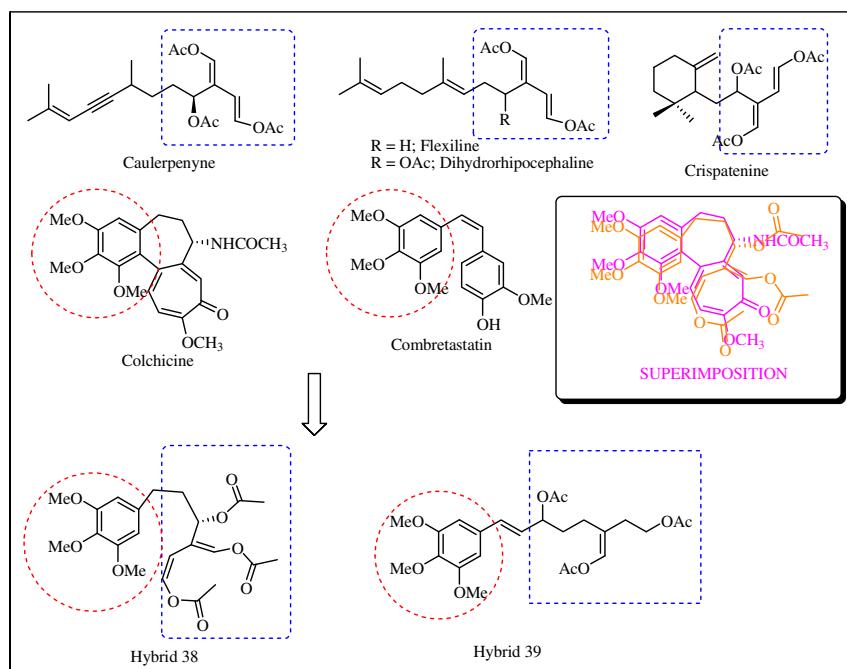
( $IC_{50} = 4.672 \mu\text{M}$ ), HCT-116 ( $IC_{50} = 0.903 \mu\text{M}$ ), MCF-7 ( $IC_{50} = 0.825 \mu\text{M}$ ), and PC-3 ( $IC_{50} = 0.813 \mu\text{M}$ ).

#### 2.1.3.8. Colchicine – adamantine conjugates with dual potential – microtubule depolymerizing and tubulin clustering activities [171].

Zefirova *et al.* synthesised Colchicine – Adamantane conjugates (Fig. 28) and tested for cytotoxicity in a cell-based assay with the human lung carcinoma cell line A549. The compounds 47–51 were found to be the most active with an  $EC_{50}$  value of  $2 \pm 1.0 \text{ nM}$ ,  $6 \pm 1.4 \text{ nM}$ ,  $5 \pm 1.8 \text{ nM}$ ,  $11 \pm 1.7 \text{ nM}$  and  $4.8 \pm 0.5 \text{ nM}$ . These compounds promoted the disassembly of microtubules followed by formation of stable tubulin clusters. To check the role of amino acid substituent in the parent structure, the synthesized compound 48, with-out N-tert-butoxycarbonyl-(2R, 3S)-phenylisoseryl moiety was investigated in detail. Hybrid 48 exhibited remarkable cytotoxicity and tubulin clustering activity indicating that the clustering effect does not depend upon the presence of taxoter amino acid side chain.

#### 2.1.4. Podophyllotoxin

Podophyllotoxin (PDT) (52), a bioactive lignan, commonly known as the American mandrake or May apple was first isolated by Podwyssotzki in 1880 from the North American Plant

**Fig. 20.** SAR of colchicines.**Fig. 21.** Colchicine-caulerpenyne hybrids.

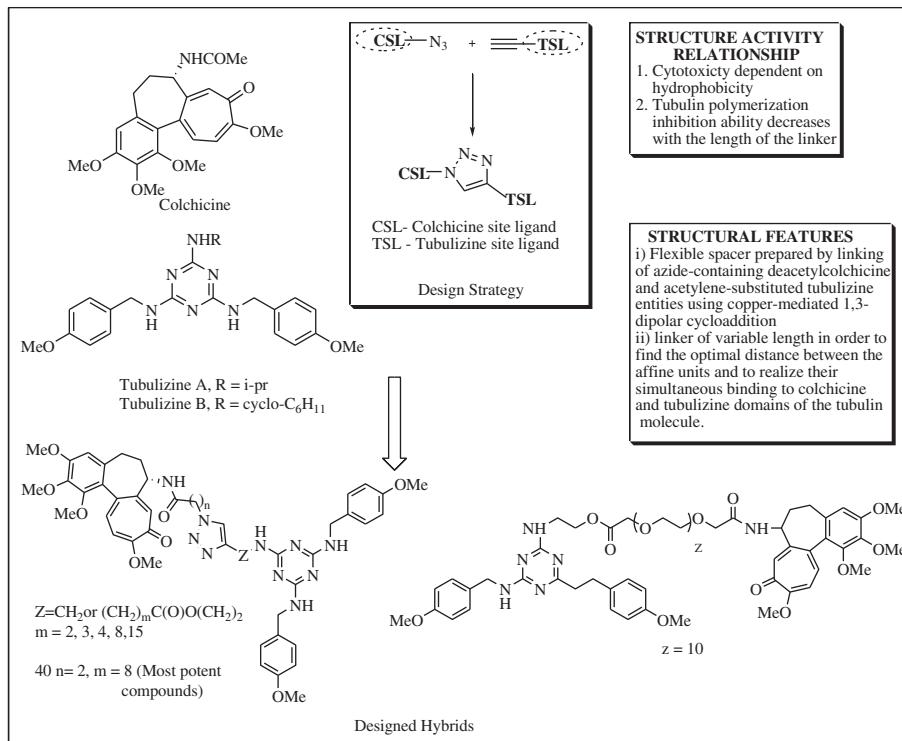


Fig. 22. Bivalent colchicines-tubulizine hybrids.

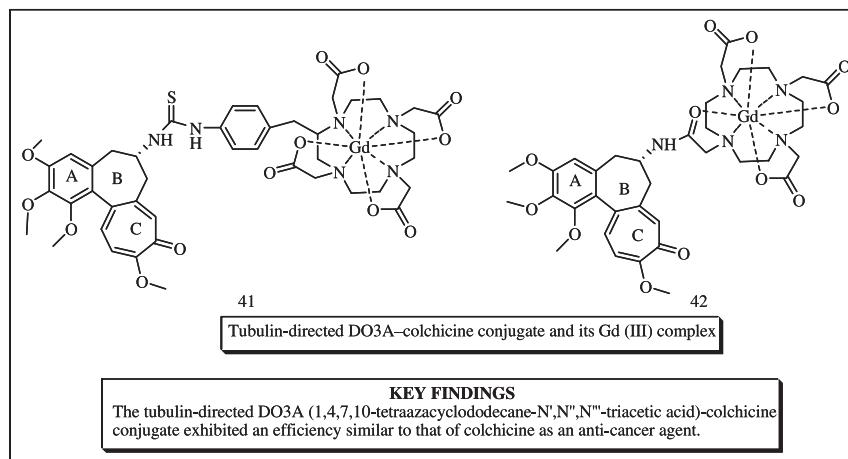
*podophyllotoxin peltatum* Linnaeus [172]. It was isolated from other species later like *P. emodi* wall and *P. Pleianthum*. Etoposide and teniposide (semis synthetic derivatives of Podophyllotoxin) are being currently used in cancer chemotherapy against various cancers [173]. The structure activity relationship of Podophyllotoxin is summarized in Fig. 29.

**2.1.4.1. Bisepipodophyllotoxins Hybrids [174].** Attempts to synthesize more potent and less toxic analogues based on podophyllotoxin rings led to the discovery of epipodophyllotoxin derivatives i.e. etoposide and teniposide [175]. Epipodophyllotoxin basically differs from podophyllotoxin as they possess hydroxy group at 4' position and also involves the change of stereochemistry from at the C4 position of basic podophyllotoxin moiety. Both podophyllotoxin as well as epipodophyllotoxin rings have been extensively explored and many structural modifications have been reported. Such investigations have led to the development of several promising drug candidates, that includes: etoposfate [176], NPF (p-fluoro at 4β-position instead of a glycol-side of etoposide) [177] and moieties and GL-331 (p-nitro anilino at 4β-position instead of a glyco-side of etoposide) [178,179]. A comparative molecular field analysis (CoMFA) and novel CoMFA/q-GRS technique [180] revealed that topo II inhibitory activity was related to three structurally distinct pharmacophoric domains. Based on these studies and promising anticancer displayed by some dimeric analogues of neutral DNA mono-intercalating agents, bis(acridine-4-carboxamide) and bibenzimidazoles as poisons for topoisomerase [181], Kamal et al. synthesised novel bisepipodophyllotoxin analogues linked at C4-position (Fig. 30). The cytotoxic assay for most of these analogues demonstrated many fold increase of activity in comparison to etoposide. The compound 54a exhibits cytotoxic potency in CNS cancer panel with GI<sub>50</sub> value of <0.01 μM. In the ovarian and CNS cancer panel growth, compound 54b exhibited GI<sub>50</sub> value of 1.56 and 0.978 μM, respectively. The

bisepipodophyllotoxins exhibited moderate to strong DNA-topoisomerase II poisoning activity.

**2.1.4.2. Lignopurines: hybrids of cyclolignans and purines [182].** Castro et al. in their attempts of chemomodulation of podophyllotoxin and its derivatives identified podophyllolic aldehyde lacking the lactone ring with selective cytotoxicity against HT-29 human colon carcinoma and certain breast and brain cancer [183]. Keeping this in view, a new family of hybrids, lignopurines was synthesised by the linkage of non-lactonic podophyllolic aldehyde and purines (possessing important biological activities) through aliphatic and aromatic chains and evaluated them against several tumor cell lines (Fig. 31). The results of the cytotoxicity studies revealed that lignopurines were slightly less cytotoxic than the parent podophyllolic aldehyde, although the selectivity was maintained or even improved. Cell cycle and confocal studies revealed that these derivatives interfere with the tubulin polymerization and arrest cells at the G2/M phase. The most potent compound 55 possessed a doubly benzylic aromatic fragment as the linker. Hybrid 55 exhibited an GI<sub>50</sub> value of 0.81 ± 0.031 μM, 0.051 ± 0.0046 μM, 0.029 ± 0.0014 μM against MB-231 (breast carcinoma) HT-29 (colon carcinoma), A-549 (lung carcinoma).

**2.1.4.3. Acrylamidopodophyllotoxin conjugates [184].** In continuation of their investigations on Podophyllotoxin and encouraging reports on anticancer activity of podophyllotoxin analogues formed by replacement of the C-4 sugar moiety of etoposide and teniposide with a non-sugar substituent [185], in particular N-linked congeners like GL-331 and NPF [186–189], Kamal et al. designed a series of 4β-acrylamidopodophyllotoxin congeners (Fig. 32), wherein the podophyllotoxin is linked to a stilbene moiety in view of the well established and reported anticancer profile of naturally occurring stilbene i.e. combretastatin A-4 [190] as well as their derivatives and analogues [191]. The synthesized derivatives were evaluated

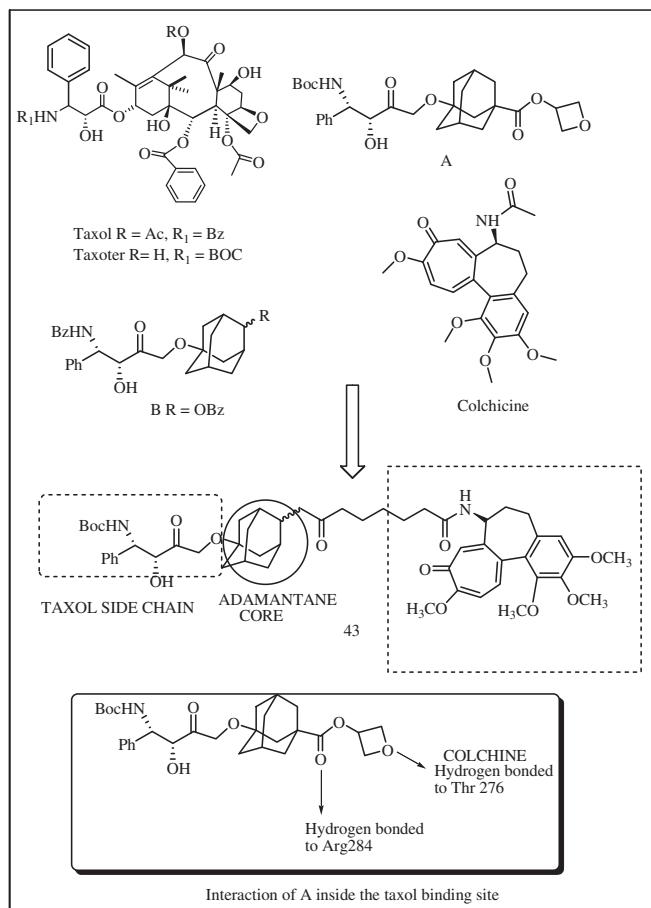


**Fig. 23.** Tubulin-directed DO3 A-colchicines conjugate.

for their cytotoxicity against five human cancer cell lines (breast, oral, colon, lung and ovarian). Some of the podophyllotoxin conjugates displayed significant cytotoxicity with conjugate 56 exhibiting promising results with  $GI_{50}$  value  $<0.1 \mu\text{M}$  against MCF-7 cell line (breast).

**2.1.4.4.  $\beta$ -alkylamidochalcone and 4 $\beta$ -cinnamido linked podophyllotoxins [192].** Encouraging reports of some podophyllotoxin analogs/derivatives [193], methoxy chalcones [194,195] and

cinnamic acid derivatives, in particular, cinnamic acid esters as antitumor agents [196,197] prompted Kamal *et al.* to design a series of 4 $\beta$ -alkylamidochalcone and 4 $\beta$ -cinnamido linked podophyllotoxin congeners (Fig. 33) by linking the chalcone and cinnamic acid moieties to the 4 $\beta$ -aminopodophyllotoxin scaffold through stable alkane spacers and amide bond formation. The hybrids were synthesised and evaluated for anticancer activity against five human cancer cell lines (A-549, A375, MCF-7, HT-29 and ACHN). *In-vitro* cytotoxicity evaluation results indicated that chalcone-podophyllotoxin conjugates (58 and 59) showed moderate activity against different cancer cell lines ( $IC_{50} = 5.3\text{--}26.7 \mu\text{M}$ ). The quinolino-chalcone linked podophyllotoxins showed promising activity with  $IC_{50}$  values ranging from 2.2 to 15.4  $\mu\text{M}$ . Most promising results were displayed by cinnamido-podophyllotoxin conjugates against A-549 cancer cell line with  $IC_{50}$  values ranging from 2.1 to 9.5  $\mu\text{M}$ . Flow cytometry analysis showed that cinnamido-podophyllotoxin conjugates arrested the cell cycle in the G2/M phase leading to caspase-3 dependent apoptotic cell death.



**Fig. 24.** Tubulin Ligands with adamantine core.

### 2.1.5. Taxols

**2.1.3. Taxols**  
Paclitaxel (Taxol) (60) and docetaxel (Taxotere) (61) (Fig. 34) binds at taxanes binding site. Paclitaxel was originally isolated and reported from the bark of the pacific yew tree *Taxus brevifolia* in 1960 and named as Taxol. Docetaxel is a semi-synthetic analog synthesized from a precursor isolated from the European yew tree *Taxus baccata*. The taxanes can be produced semi synthetically and are clinically used for the treatment of breast, ovarian, prostate and non-small cell lung cancer. At high concentration, the taxanes act through microtubule stabilization and at low concentrations, suppression of the dynamic instability of microtubules causing mitotic arrest leads to apoptosis occurs [198,199].

**2.1.5.1. Paclitaxel-chlorambucil hybrids [200].** Wittman *et al.* in view of proved synergism by taxol with other anti tumor agents and reports of hypersensitivity of paclitaxel resistant cell lines to cisplatin designed hybrid molecules combining an alkylating agent with paclitaxel to extend the therapeutic utility of paclitaxel to resistant tumors. The paclitaxel-chlorambucil hybrids (Fig. 35) were synthesised and evaluated *in vitro* for inhibition of Tubulin polymerization and cytotoxicity against the HCT-116 human colon tumor cell line. The hybrids were also tested *in vivo* using the M109 Madison murine lung carcinoma M109 tumor model. Hybrid 62 displayed excellent *in vivo* antitumor activity in M109 and the

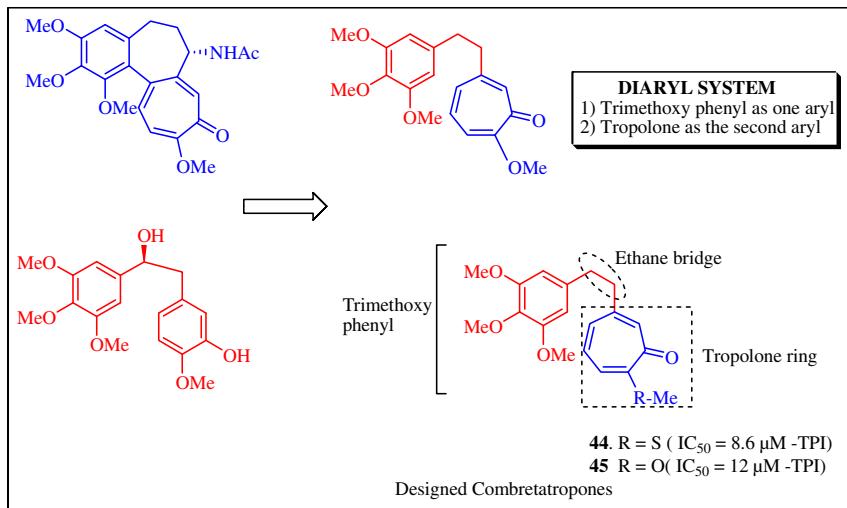


Fig. 25. Combretatropones – hybrids of combrestatins and colchicines.

paclitaxel resistant M109/tax1R models that were superior to single agent or combination therapy.

#### 2.1.5.2. Discodermolide-paclitaxel hybrids [201]

(+)-Discodermolide, a potent antitumor polyketide natural product, isolated from extracts of the Caribbean marine sponge

*Discodermia dissolute* has been recently reported to bind to a region close to the paclitaxel binding site and causes accelerated cell senescence. Discodermolide and paclitaxel are known to act synergistically in cell culture as well as ovarian xenograft tumor model in nude mice and this synergism has been assumed due to their ability to induce stability on opposite sides of microtubule interface

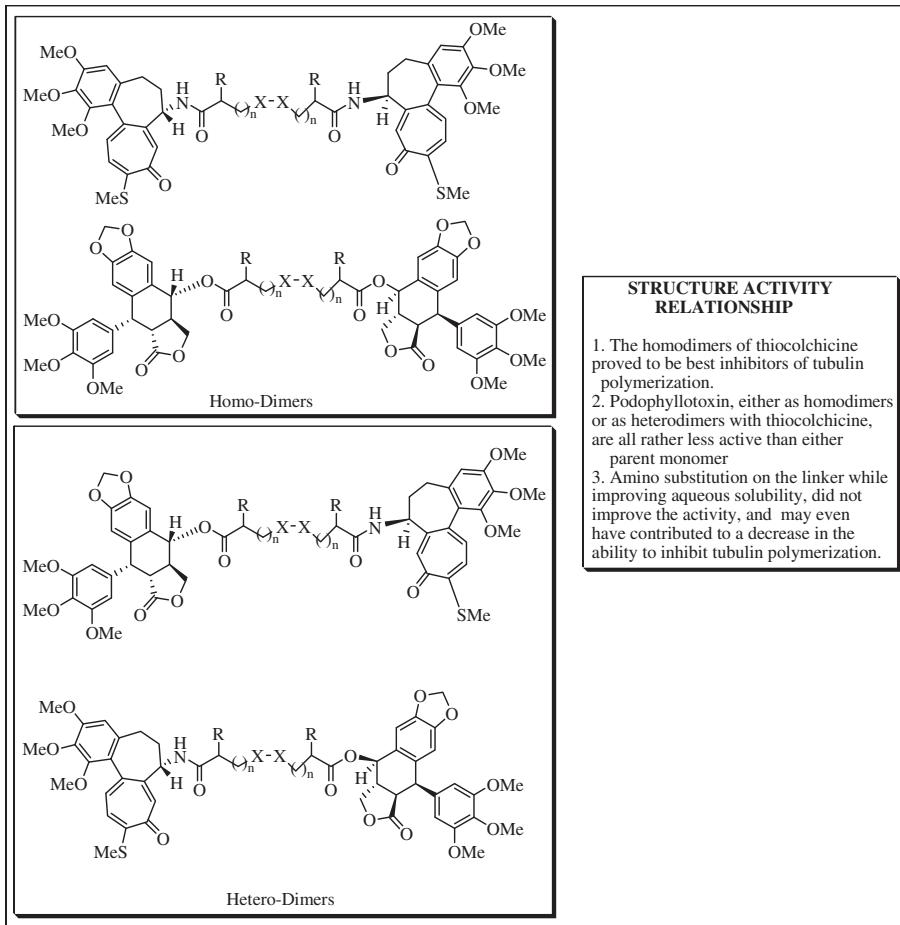
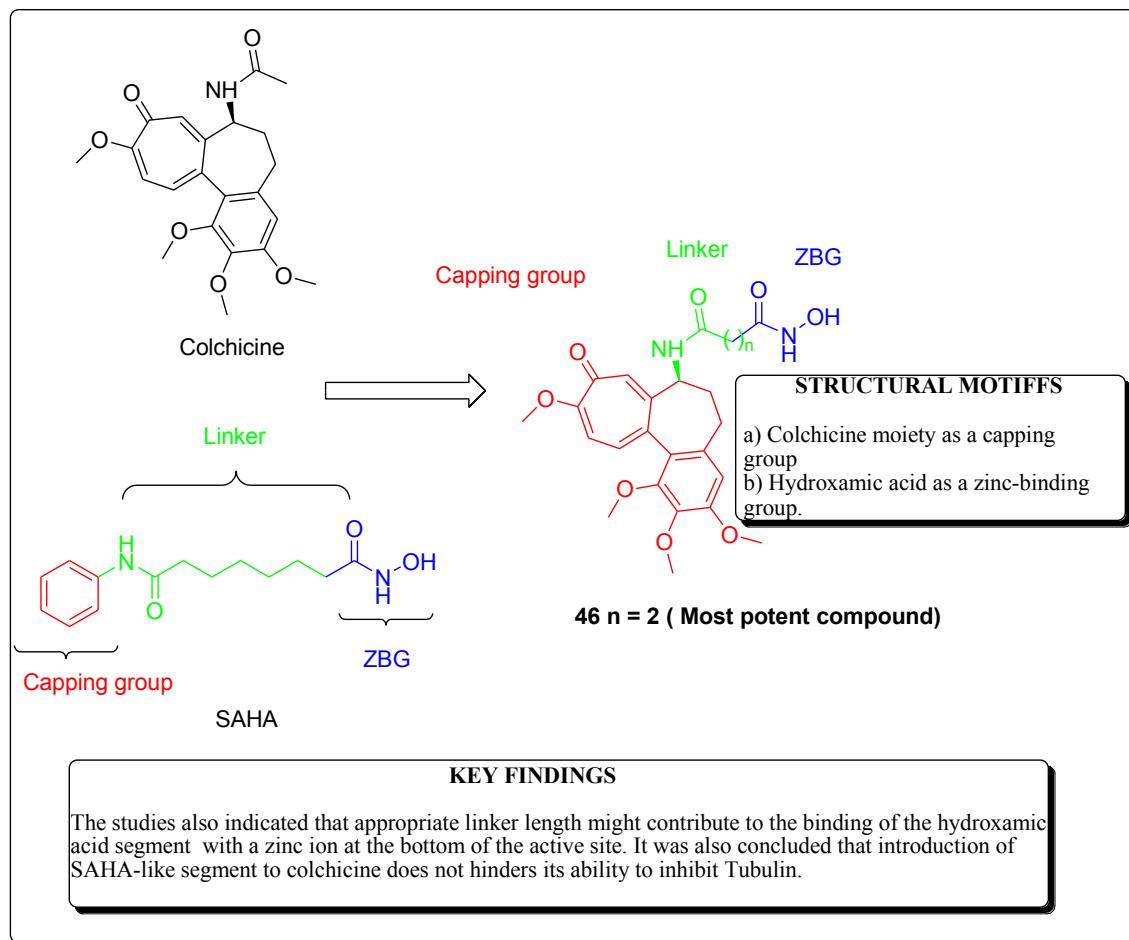


Fig. 26. Thiocolchicine-podophyllotoxin conjugates.



**Fig. 27.** Colchicine-SAHA hybrids.

[202–206]. Smith *et al.* with the aid of computational studies identified the binding modes of Discodermolide at the paclitaxel binding site of Tubulin and revealed that the aromatic pocket occupied by the paclitaxel side chain is not occupied by Discodermolide. Different docking poses were observed for discodermolide. The docking poses indicated that the filling of the aromatic pocket in the vicinity of carbamate group of discodermolide which is occupied by the phenyl group in case of paclitaxel can prove beneficial in potentiating the antiproliferative action. Keeping this in view, Smith *et al.* designed discodermolide hybrids (Fig. 36), through a linker of suitable length. The hybrids were evaluated for antiproliferative activity against human lung (A549) and breast (MCF-7) cancer cell lines. Biological evaluation reveals a two- to eight-fold increase in antiproliferative activity compared to the parent molecule using the A549 and MCF-7 cancer cell lines. It was also observed that all the hybrids increased the amount of microtubule polymerization indicating that all of them were acting through the same mechanism. Hybrid 63 was found to be the most active against A-549 with IC<sub>50</sub> value of 1.05 nM.

#### 2.1.6. Vinca alkaloids

The isolation of vinca alkaloids, vinblastine (64, GI<sub>50</sub> = 9.98 × 10<sup>-2</sup> M) and vincristine (65, GI<sub>50</sub> = 3.14 × 10<sup>-7</sup> M) [207] (Fig. 37) from the Madagascar periwinkle, *Catharanthus roseus*, established a new era of the use of plant material as anti-cancer agents. Vinca alkaloids are the most widely recognized member of the class of bisindole alkaloids as a result of their clinical

use in cancer. They were the first agents to advance into clinical use for the treatment of cancer.

**2.1.6.1. Vinca – phomopsin hybrids [208].** Knossow and co-workers [209] reported the X-ray structure of vinblastine bound to the tubulin-colchicine: RB3-SLD complex ((Tc) 2R) with a resolution of 4.1 Å. This binding site is at the interface between two tubulin heterodimers in a head-to-tail arrangement, and vinblastine is oriented so that its cleavamine and vindoline moieties each interact with both heterodimers. The authors also showed that the vinblastine site in this complex is very similar to the vinblastine site in tubulin. Earlier the authors reported the X-ray structures of phomopsin A (hexapeptide containing a 13-membered cyclic core). Superimposition of both binding sites revealed that they significantly overlap, however, the vindoline moiety of vinblastine and the lateral chain of phomopsin A are oriented in opposite directions. This led to the design of hybrids of vinblastine and phomopsin that may interfere with both binding sites leading to an increased cytotoxicity (Fig 38). Ten hybrids of vinca alkaloids and phomopsin A have been synthesized by linking the octahydrophomopsin lateral chain to the tertiary amine of the cleavamine moiety of anhydrovinblastine (AVLB) and vinorelbine. Most of them were found to be potent inhibitors of microtubules assembly and displayed good cytotoxicity against KB cell line.

**2.1.6.2. Vindoline – Thicolchicine hybrid [210].** In search of non toxic and selective tubulin inhibitors, Passarella *et al.* explored the

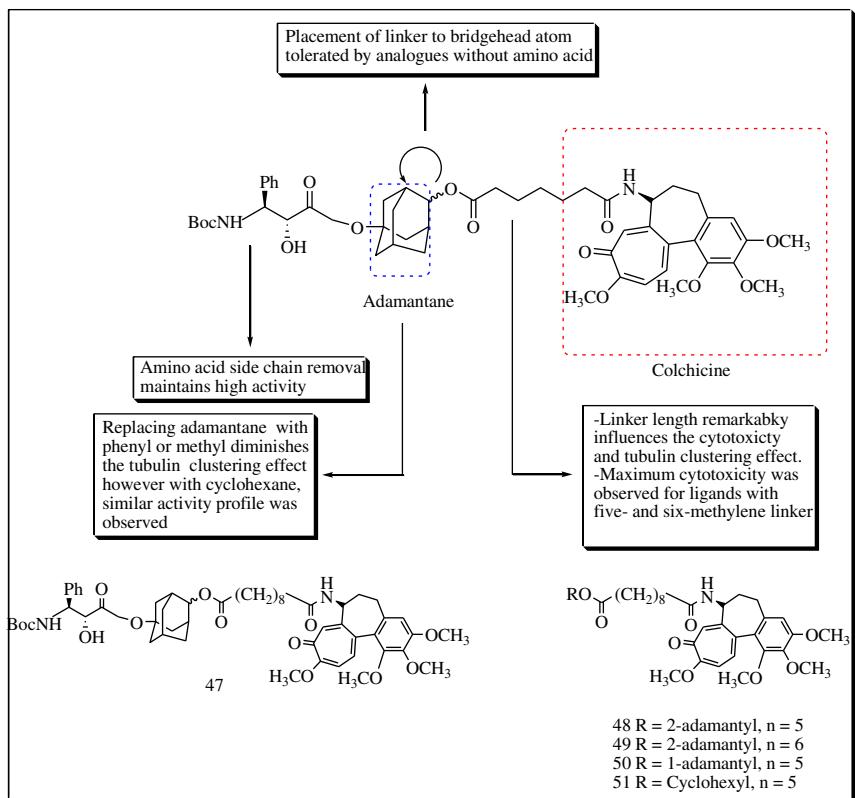


Fig. 28. Colchicine-adamantane conjugates.

concept of multivalency to synthesize a series of novel hybrid compounds obtained by the attachment of anhydrovinblastine, vinorelbine, and vindoline to thiocolchicine, podophyllotoxin, and baccatin III (Fig. 39). Two types of diacyl spacers were introduced. The hybrids were evaluated for their ability to affect the tubulin polymerization the anticancer activities were examined in human lung carcinoma A549. Compound 66 displayed the ability to inhibit tubulin polymerization, and was more effective as an anti-proliferative agent than thiocolchicine. Detailed investigation of Compound 66 confirmed that the i) ratio of unpolymerized/polymerized tubulin increases in a dose-dependent manner in the presence of Compound 66 and thiocolchicine ii) its interaction with tubulin and cell cycle arrest at the G2/M phases.

## 2.2. Isatin based hybrids

The isatin (1H-indole-2, 3-dione) is a privileged scaffold with wide possibility for chemical modification and broad spectrum of biological properties [211]. Among these properties, cytotoxic and antineoplastic activities have been found to be interesting and mechanistically can be associated with its affinity to inhibit tyrosine kinase [212] and serine/threonine-specific protein kinases such as the cyclic-dependent kinases (CDKs) [213] and carbonic anhydrase isozymes (CAIs) [214]. This ability of isatin to act as tumor poison by inhibiting multiple enzymes makes them one of the explored functionality for the design of bifunctional hybrids.

### 2.2.1. Uracil-isatin conjugates and their cytotoxic evaluation [215]

Proved anticancer potential of both uracil [211] and isatin [212–214] led to the design of triazole tethered uracil-isatin conjugates via click chemistry. Numerous reports on the cytotoxic potential of triazoles [216] have attracted the researchers towards their

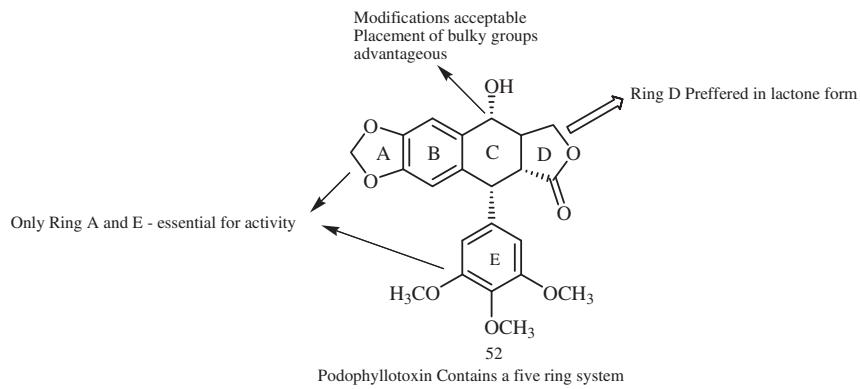
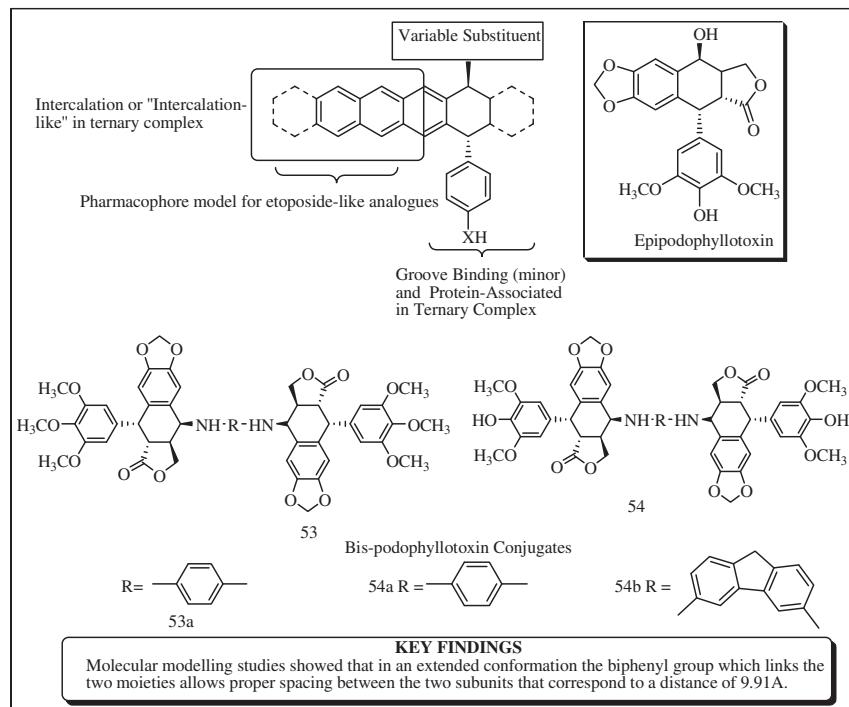
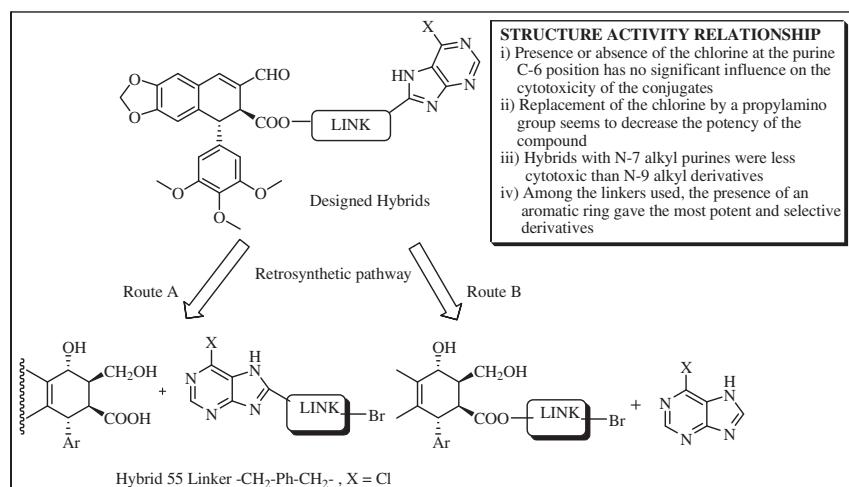
selection as a linker for the two functionalities. Apart from this, they also confer properties like moderate dipole character, hydrogen bonding capability, rigidity and stability under *in vivo* conditions [217]. The designed conjugates (Fig. 40) were evaluated for cytotoxic activity against three human cancer cell lines, HeLa (cervix), MCF-7 (breast) and DU145 (prostate) using MTT assay. The evaluation studies revealed the dependence of cytotoxicity on C-5 substituents of both uracil and isatin as well as the alkyl chain length with compounds 68 and 69 showing IC<sub>50</sub> values of 18.21 and 13.90 μM respectively against DU145 cell lines. Compound 68 was selectively toxic towards DU145 while 69 in addition to DU145 exhibited cytotoxicity against Hela cell line also with an IC<sub>50</sub> value of 33.08 μM.

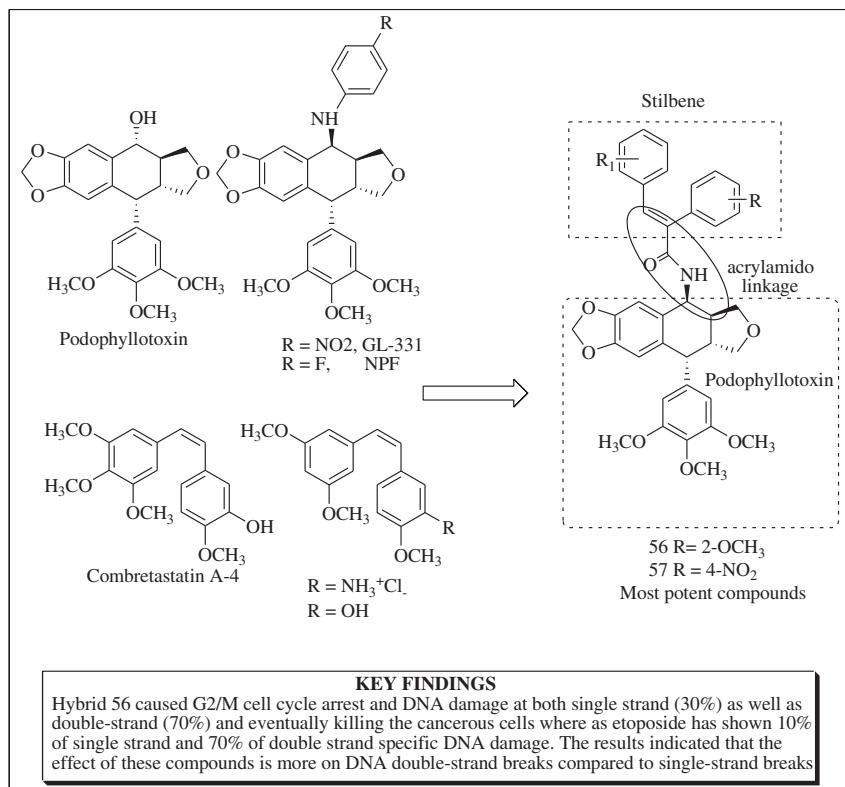
### 2.2.2. Triazole tethered isatin conjugates [218]

The success of halogenated isatins, 5-Bromo-3-O-nitrophenyl isatin hydrazone, 5-bromo-(2-oxo-3-indolinyl) thiazolidine-2,4-diones substituted by various Mannich bases [219], isatin-pyrazoline/thiazolidinone conjugates as anticancer agents led to the design and synthesis of novel 1H-1,2,3- 3-triazole tethered isatin conjugates via azide-alkyne cycloaddition. The conjugates were evaluated for cytotoxicity against four human cancer cell lines viz. A-549 (lung), PC-3 (prostate), THP-1 (leukemia) and Caco-2 (colon) using sulforhodamine B assay. Compound 70, 71, 72, 73 proved to be twice as potent as 5-fluorouracil against THP-1 cell line with 70 and 71 being most active exhibiting IC<sub>50</sub> values of <1 μM against all cell lines except Caco-2. The design strategy along with the structural features preferred are represented in Fig. 41

### 2.2.3. Isatin-benzothiazole analogs [220]

Tyrosine kinase inhibitory and antiangiogenic properties of oxoindole derivatives of indole based molecules i.e. semaxanib,

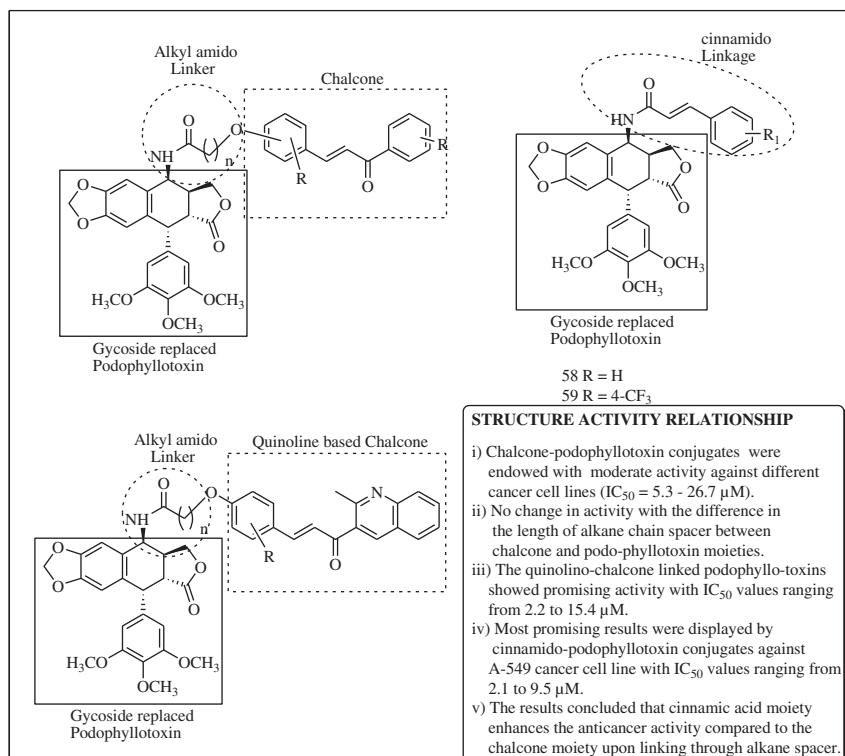
**Fig. 29.** Structure activity relationship of podophyllotoxin.**Fig. 30.** Bisepipodophyllotoxins hybrids.**Fig. 31.** Hybrids of cyclolignans and purines.



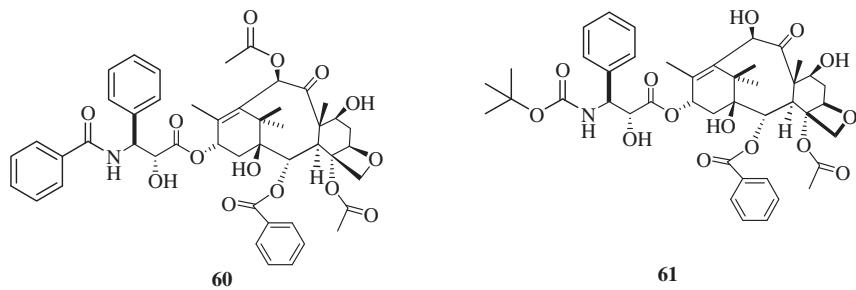
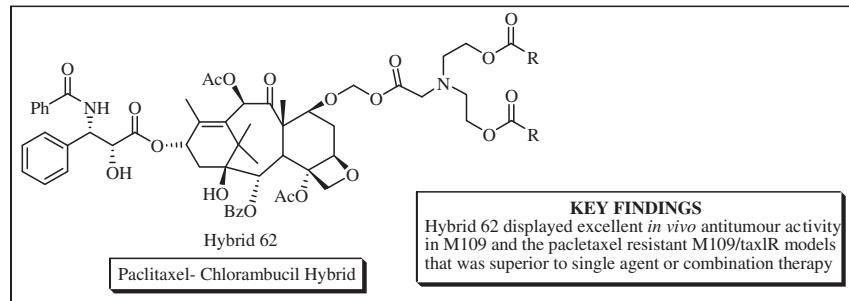
**Fig. 32.** Acrylamidopodophyllotoxin conjugates.

Sunitinib) and CDK inhibitory properties of isatin derived phenylhydrazones [221] along with antitumor properties of 2-indolone imino [211] led to the fusion of isatin ring system with the benzothiazole ring system by a Schiff base reaction.

Linkage of benzothiazole was done in view of the anticancer activity of Phortress benzothiazole prodrug against xenografts [222]. Thus a hybrid pharmacophore approach was used to design and synthesize isatin–benzothiazole analogs (Fig. 42) for



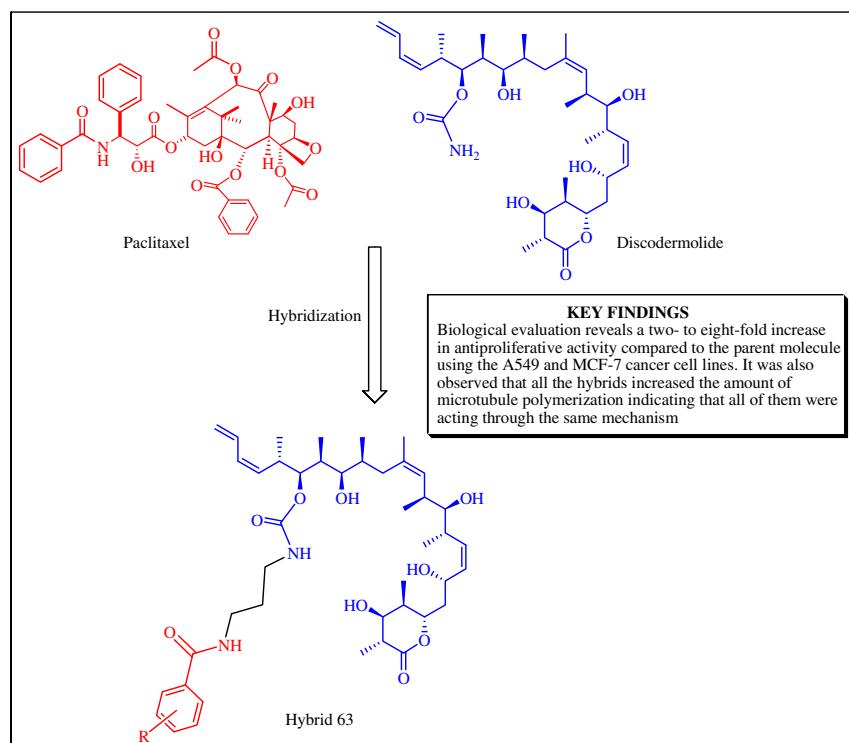
**Fig. 33.** 4β-alkylamido chalcone and 4β-cinnamido linked podophyllotoxins.

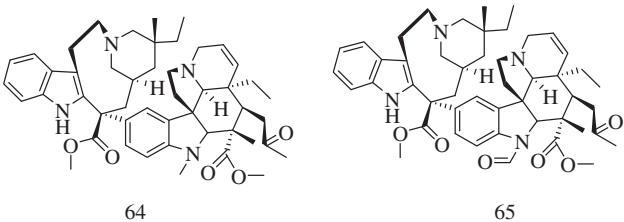
**Fig. 34.** Paclitaxel (taxol) and docetaxel (Taxotere).**Fig. 35.** Paclitaxel-chlorambucil hybrids.

evaluation of their anti-breast cancer activity against three different human breast tumor cell lines, MDA-MB231, MDA-MB468, MCF7, and two non-cancer breast epithelial cell lines, 184B5 and MCF10A. Significant cytotoxicity was displayed by most of the compounds of the series with hybrid 74 emerged as the most active. Hybrid 74 was endowed with  $GI_{50}$  value of  $19.76 \pm 0.23 \mu\text{M}$  (MDA-MB231),  $17.61 \pm 0.19 \mu\text{M}$  (MDA-MB468),  $14.56 \pm 0.21 \mu\text{M}$  (MCF7).

#### 2.2.4. Isatin-4-pirazinylquinoline hybrids [223]

The cancer cell killing effects of chloroquine [224] and its analogs indicating the anticancer potential of 4-amino quinoline ring system [225–227], anti-breast cancer activity of isatin-benzothiazole [228] and success of thiosemicarbazones against several leukemia and multidrug resistant cell lines [229–231] led to the design of hybrid compounds by linking the main structural unit of the 4-piperazinylquinoline ring system with the isatin ring

**Fig. 36.** Discodermolide-paclitaxel hybrids.



**Fig. 37.** Vincristine and vinblastine.

system (Fig. 43). The hybrids were evaluated for their cytotoxic effects on two breast cancer cell lines, MDA-MB468 (a PTEN defective, p53 positive, EGFR positive breast adenocarcinoma cell line) and MCF7 (p53+/-, invasive ductal breast carcinoma) and two non-cancer breast epithelial cell lines, 184B5 and MCF10A). The hybrids 75 and 76 were found to be most active with hybrid 75 displaying  $GI_{50}$  values of  $15.88 \pm 0.15 \mu\text{M}$  (MDA-MB 468) and  $15.12 \pm 0.34 \mu\text{M}$  (MCF7) and 76 with  $GI_{50}$  values of  $23.04 \pm 0.86 \mu\text{M}$  (MDA-MB 468),  $21.56 \pm 0.69 \mu\text{M}$  (MCF7). Flow cytometric analysis showed that the hybrids induced the cell death by apoptosis.

#### 2.2.5. Isatin-thiazolidinone hybrid [232]

Inhibition of tyrosine kinases by thiazolidinone moiety [233] and apoptosis inducing ability of 5-benzylidene-2-phenylimino-1,3-thiazolidin-4-one has been well reported [234]. Cytotoxic  $\pi$  electron delocalized lipophilic cations (DLCs) possess marked and selective antitumor activity. This effect of DLCs is because of their selective accumulation in negatively charged mitochondria in carcinoma cells due to electrochemical proton gradient [235–241]. Structural requirements of 4-oxothiazolidine and double conjugate system has been reported to be essential for the  $\pi$  electron delocalization activity [242]. In view of tumor therapeutic potential of isatin and thiazole groups, hybrids of the two were synthesized maintaining the unique double conjugate structure (Fig. 44) and evaluated them for their cytotoxic and cytostatic activities. The acute toxicity studies in mice models revealed that these analogues possess low systemic toxicity and are safe up to 1600 mg/kg. Among the compounds hybrid 77 was found to be the most active, which induced S phase arrest in cell cycle in a time dependent manner. Hybrid 77 was most effective in breast cancer cell lines

(MDA MB 231 and MDA MB 435) with  $IC_{50}$  values ranging from  $51 \mu\text{M}$  to  $63 \mu\text{M}$ .

### 2.3. Coumarin based hybrids

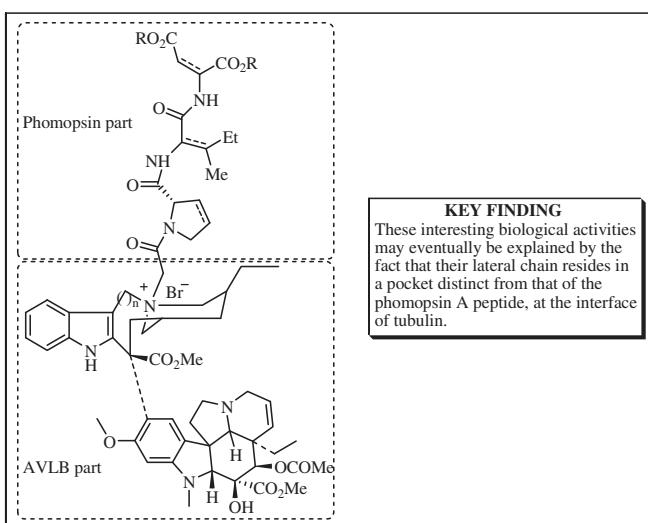
Coumarins form an important class of compounds, which occupy a special role in nature. They belong to the flavonoid class of plant secondary metabolite, which have been found to exhibit a variety of biological activities, usually associated with low toxicity and have raised considerable interest because of their potential beneficial effects on human health [243,244]. The presence of coumarin architecture in naturally occurring products and their wide-range applications in agrochemicals, drugs and pharmaceuticals [245,249] such as anticancer [250,251], anti-HIV [252], anti-tuberculosis [253], anti-influenza [254], anti-alzheimer [255,256], anti-inflammatory [257], antiviral [258] and antimicrobial agents [259] makes it a privileged structure. Though coumarin possesses diverse array of biological activities but their ability to kill cancer cells through varied mechanisms is the prime reason for their inclusion in the hybrids framework.

#### 2.3.1. Coumarin-pyrazoline hybrids endowed phenyl sulfonyl moiety [260]

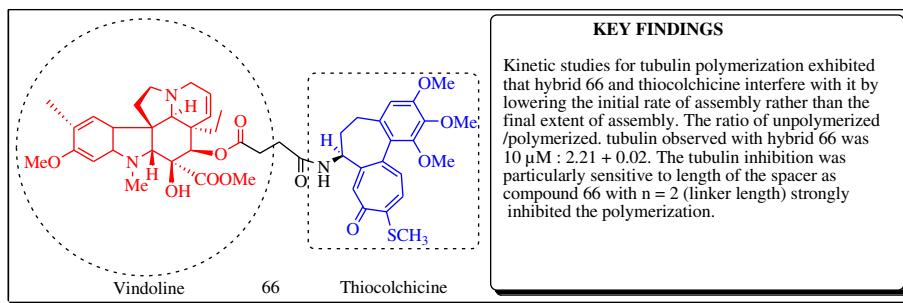
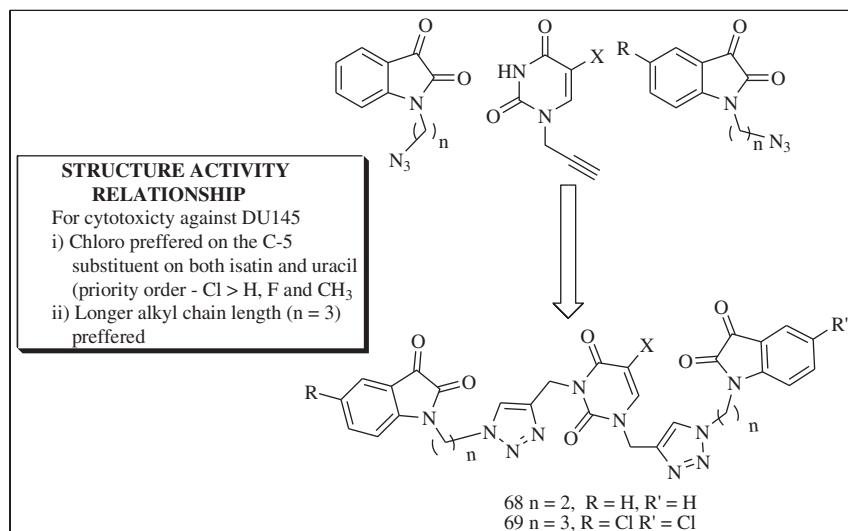
Amin et al adopted hybridization and bioisosterism based approach for the design of pyrazoline hybrids comprising two types of substitution patterns; one bearing phenylsulfonyl entities while the other type had a terminal sulfamoyl moiety. The compounds were designed via bioisosteric replacement of imidazo fused pyridine with coumarin utilizing a patented imidazo fused pyridine-pyrazoline hybrid (Fig. 45). The criterion for the selection of the functionalities were as follows: i) 7-methoxy-8-substituted coumarin, present in Osthole II, a coumarin based agent possessing potent activity against lung cancer A549 cells and breast cancer cells by arresting cell cycle in G2 phase followed by induction of apoptosis through modulation PI3K/Akt pathway ii) success of pyrazoline ring displaying potent and selective activity in the NCI 60 human cancer cell lines panel. iii) inhibitory potential of N-phenylsulfonyl pyrazoline derivatives exhibiting high activity against human gastric cancer cell SGC-7901, liver cancer Hep-G2 and human prostate PC-3 cell lines telomerase inhibition. iv) ongoing clinical trials of several sulfonamides as antitumour agents. The target compounds were obtained by cyclization of the coumarin chalcones with various substituted hydrazines to produce the corresponding pyrazolines through 1,4-addition on  $\alpha,\beta$ -unsaturated carbonyl system. Selected compounds were investigated for their anticancer activity toward 60 cancer cell lines according to US NCI protocol where breast cancer MCF7 and colon cancer HCT-116 were the most susceptible to the influence of compounds 78, 79, 80 with 80 possessing highest cytotoxicity proved to have weak enzyme inhibitory activity against PI3K (p110a/p85a). Compound 80 possessed  $IC_{50}$  of  $0.01 \mu\text{M}$  against HCT-116 ( $IC_{50}$  of Doxorubicin =  $0.63 \mu\text{M}$ ). Class I compounds displayed better cytotoxic potential than Class II.

#### 2.3.2. Coumarin-stilbene hybrid compounds: identification of novel proapoptotic agents [261]

Resveratrol (3,5,4-trans-trihydroxystilbene), a naturally occurring polyphenol found in large amount in grapes [262] has gained enough attention due to its wide array of biological activities [263]. Structure activity relationship on resveratrol analogues revealed i) the presence of a number of methoxy groups on the phenyl rings remarkably influenced the antitumour and proapoptotic activity ii) 3,4',5,4 tetramethoxystilbene proved to be beneficial for inhibition of the cancer cell growth [264–266]. This tempted the authors towards their fusion with the privileged heterocyclic nucleus i.e.



**Fig. 38.** Vinca-phomopsin hybrids.

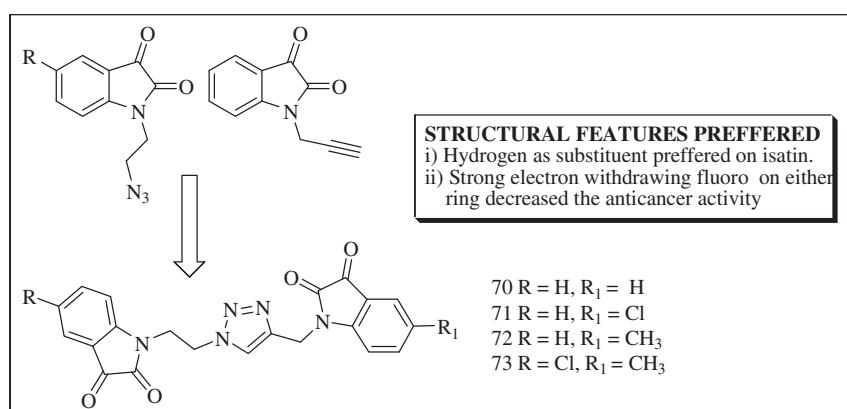
**Fig. 39.** Vindoline-thiocolchicine hybrid.**Fig. 40.** Uracil-isatin conjugates.

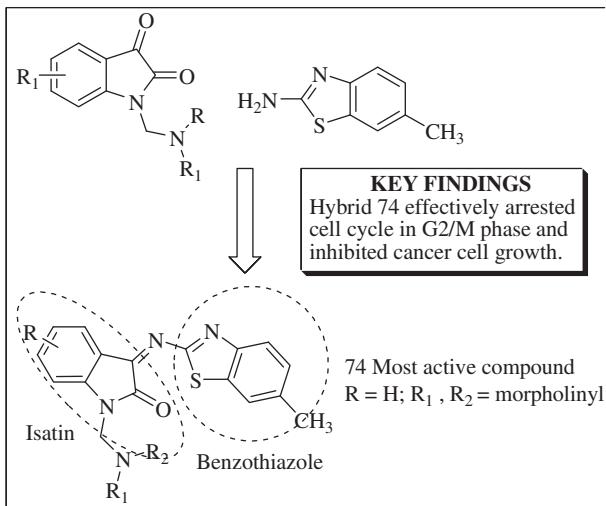
coumarins by insertion of a properly substituted trans-vinylbenzene moiety on a coumarin backbone (Fig. 46). The synthesized analogues were initially tested for their antiproliferative activity in H460 cells. The potent compounds 81 and 82 (more potent than resveratrol) were also evaluated against A431 and JR8 cells and investigated in detail to explore the cellular basis of their antitumour properties. The IC<sub>50</sub> values of compound 81 was 0.45  $\mu$ M (lung cancer cells H460), 3.44  $\mu$ M (squamous cell carcinoma A431), 3.2  $\mu$ M (melanoma JR8) and the IC<sub>50</sub> values of

compound 82 was 0.29  $\mu$ M (lung cancer cells H460), 3.5  $\mu$ M (squamous cell carcinoma A431), 3.5  $\mu$ M (melanoma JR8).

### 2.3.3. Coumarin-benzimidazole hybrids [267]

The existence of benzimidazole moiety in many biologically active natural products, synthetic compounds [268] and their clinical potential toward tumor cells [269–271] and as antiviral agents [272–275] is well explored. Keeping in view, the proved anticancer potential of benzimidazole and coumarins [276,277],

**Fig. 41.** Triazole tethered isatin conjugates.



**Fig. 42.** Isatin-Benzothiazole analogs.

coumarin-benzimidazole hybrids were earlier synthesised via a spacer linked approach and were found to possess significant clinical potential such as anti-angiogenesis and antihepatitis [278,279]. With this background, Paul *et al.* designed and synthesised a novel series of 3-(1H-benzo[d]imidazol-2-yl)-7-(substituted amino)-2H-chromen-2-one derivatives by direct fusion of coumarin and benzimidazole without any linker (Fig. 47). The synthesized compounds were screened for *in vitro* antitumor activity against preliminary 60 tumor cell lines panel assay. Compound 83 exhibited significant inhibition for cancer cells (more than active known drug 5-fluorouracil (in some cell lines). Compound 83 displayed appreciable anticancer activities against leukemia, colon cancer and breast cancer cell lines. The molecular properties of compounds were calculated. Compound 83 (most active of the series) was endowed with higher TPSA and lower log P and molar refractometry which indicated that lipophilicity and molar refractometry of the molecules were not crucial factors for the activity whereas hydrophilicity played the key role for anti-tumor activity. Compound 83 was docked in the active site of topoisomerase, ribonucleotide reductase and dihydrofolate reductase (DHFR) containing NADPH and folate. Docking of compound in the active site of these enzymes indicated the probable mode of action for anticancer activities. Both experimental evidence and computational studies indicated that the introduction of ethanolamine at position-7 of compound remarkably influences the cytotoxic potential. Leukemia cells HL-60 (TB), CCRF-CEM, K-562, MOLT-4 and RPMI-8226 proved to be selectively sensitive toward compound 83 with growth inhibition of 80.51%, 72.52%, 57.34%, 46.65% and 38.03% respectively, breast cancer cells T-47D, MDA-MB-231/ATCC, MDA-MB-468, BT-549 with GI values 70.68%, 58.91%, 48.37% and 33.10% respectively, colon cancer cells HCT-15 and HCT-116 with GI values 72.67% and 62.25%, Malonema cancer cell LOX IMVI and prostate cancer cell PC-3 GI value of 54.29% and 56.69% respectively.

#### 2.3.4. Coumarin – chalcone hybrid [280]

Sashidhara *et al.* also employed the pharmacophore molecular makeup approach for designing coumarin-chalcone hybrids (Fig. 48). The designed molecules possessed the following structural features i) Chalcone framework (1,3-diaryl-2-propenone) which possesses diverse array of biological activities, in particular, antitumour. (ii) Coumarin skeleton or naphthopyran ring [core structural unit present in neo-transhinlactone (earlier reported to

posses excellent inhibitory potential against human breast cancer cell line [281–285]. With this background and recently reported coumarin-chalcone hybrids as potent tumour inhibitory agents, a series of coumarin–chalcone hybrids was synthesized and evaluated for their *in vitro* cytotoxicity against KB (oral squamous cell carcinoma), C33A (cervical carcinoma), MCF-7 (breast adenocarcinoma), A549 (lung) and one normal fibroblast NIH3T3 (mouse embryo fibroblast). Compounds 84–86 showed IC<sub>50</sub> range from 3.59 to 8.12 μM. Compound 86 proved to be the most promising with 30 folds more selectivity towards C33A (cervical carcinoma) cells over normal fibroblast NIH3T3 cells (IC<sub>50</sub> value of 3.59 μM).

### 2.3.5. Coumarin–manosterol hybrids [286]

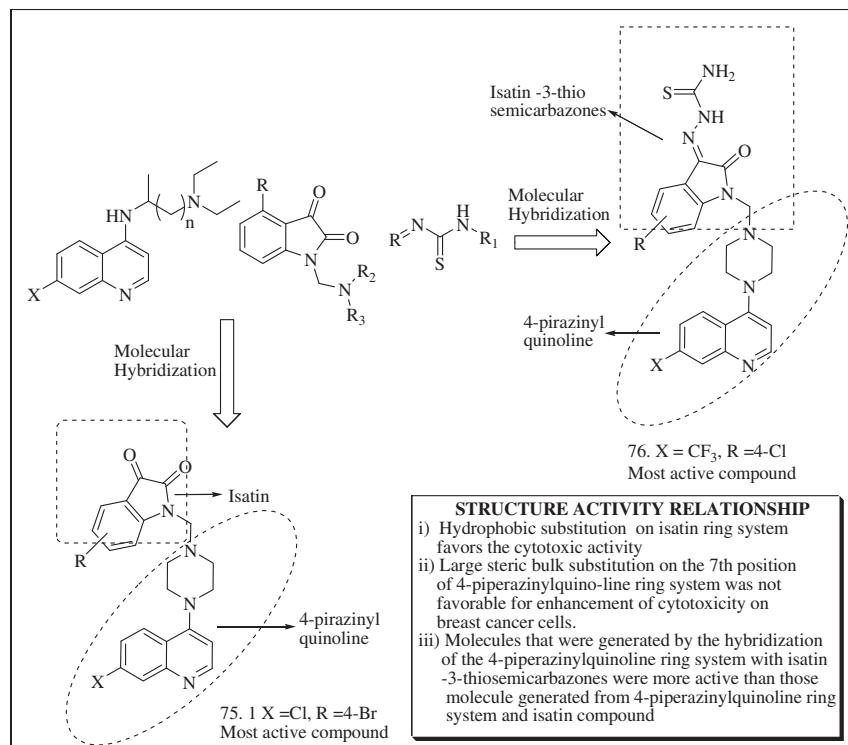
In view of the facts that breast cancer is one of the leading cause of cancer deaths [287,288] in woman today and drug resistance to the most widely used antiestrogenic agent tamoxifen [289], failure of combination therapy involving tamoxifen [290] with other cytotoxic agents and in search for novel and potent antibreast agents with new mechanisms of action, Sashidhara *et al.* discovered a novel class of coumarin-monastrol hybrid (Fig. 49), as breast cancer agents which selectively induced apoptosis in both primary and metastatic breast cancer cell lines. The selection of functionalities for the design of hybrids was done on the basis of i) Promising results observed with neo-tanshinlactone, (coumarin containing compound) exhibiting 10 folds more potent and 20 folds selective inhibitory activity against two ER human breast cancer cell lines than tamoxifen [291]. ii) Identification of monastrol (dihydropyrimidinone) as a novel cell permeable molecule that caused mitotic arrest by blocking bipolar mitotic spindle in mammalian cancer cell lines [292]. The designed hybrids were evaluated for *in vitro* anticancer activity against cancerous and non-cancerous cells. Breast cancer cell lines (MCF-7, T47D and MDA-MB-231), lung cancer cell line (A549), Human prostate lines (PC-3 and DU-145), Human hepatocellular liver carcinoma cell line (HepG2) as well as noncancerous cells (NIH3T3, HEK-293 and isolated primary mouse skin fibroblasts) were employed for the study. Among the synthesised hybrids, compound 87 significantly inhibited the proliferation of MCF-7 ( $IC_{50} = 2.4 \mu\text{M}$ ), T47D ( $IC_{50} = 3.1 \mu\text{M}$ ) and MDA-MB-231 ( $IC_{50} = 3.9 \mu\text{M}$ ) breast cancer cell.

#### **2.4. Steroidal hybrids**

Utilization of steroids as biological carrier vector for anticancer drugs in hybrid structure based drug design has gained enough attention in the recent years. Many cytotoxic drugs have been successfully linked to steroid carriers and the conjugates have displayed encouraging and promising results. Earlier studies on such hybrids revealed that cytotoxic moiety dictates the mechanisms of antitumor action while the steroid vector facilitates the internalization of the drug.

#### 2.4.1. Estradiol-chlorambucil hybrids [293]

Uses of aromatase inhibitors or estrogen sulfatase inhibitors, pure estrogen antagonists such as fulvestrant or selective estrogen receptor modulators (SERMs) such as tamoxifen are some of the possible therapies for breast cancer [294–298]. Gupta *et al.* synthesised estradiol-chlorambucil hybrids (Fig. 50) as anticancer drugs for site-directed chemo-therapy of breast cancer. Chlorambucil is an alkylating agent of the nitrogen mustard group and is used as cytostatic drug in cancer therapy [299]. The design strategy involved linking of chlorambucil to the estradiol derivative at position 16 $\alpha$ . Linkage at this position does not affect the binding mode of estradiol. The hybrids were evaluated for their *in vitro* cytotoxic activity using estrogen receptor positive (MCF-7) and negative (MDA-MB-436, MDA-MB-468, MDA-MB-231) breast cancer cell

**Fig. 43.** Isatin-4-pirazinylquinoline hybrids.

lines. Among the synthesised hybrids, Hybrid 88a showed significant cytotoxic activity with  $IC_{50} = 40 \mu\text{M}$  as compared with chlorambucil (2) ( $IC_{50} > 160 \mu\text{M}$ ) on MDA-MB-436 cell line.

#### 2.4.2. Geldanamycin-estradiol hybrid [300]

Geldanamycin (GDM) isolated from *Streptomyces hygroscopicus* is known to exert its biological effects by binding to the highly conserved N-terminal ATP binding pocket of the molecular chaperone Hsp90 [301–303]. This binding leads to degradation of several important signaling proteins resulting in cell Death. This property of geldanamycin limits its medicinal use due to significant toxicity. With the aim of designing selective GDM derivative active against particular proteins, Kuduk *et al.* in 1999 synthesised Geldanamycin-estradiol hybrids and evaluated for their ability to induce the selective degradation of the estrogen receptor (ER). The design strategy involved linkage of GDM at C-16 position via a linker keeping intact the stereochemistry at C16 i.e.  $\alpha$  necessary for high ER binding affinity. As per earlier reports, the C-17 methoxy of the benzoquinone undergoes smooth Michael-like reaction with amines. However structure activity relationship established earlier revealed that C-17 can tolerate substitutions. Thus the hybrids were constructed in a stereoselective fashion at C-16 of estradiol (Fig. 51), in a way that it could further be elaborated to a terminal primary amino group for coupling to GDM. The effect of GDM and hybrids on the steady-state levels of HER2, ER, and Raf-1 in MCF7 breast

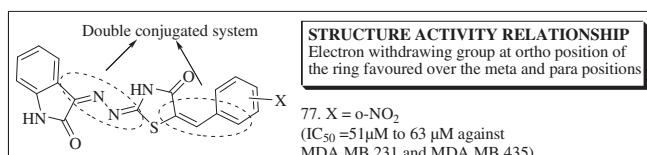
cancer cells was evaluated. The constructs were found to be more active and more selective than the parent causing degradation of ER and HER2 with hybrid 89 exhibiting an  $IC_{50}$  value of  $0.1 \mu\text{M}$  against HER2 (transmembrane kinase that is amplified and over expressed in a significant number of breast cancers),  $0.08 \mu\text{M}$  against ER (estrogen receptor) and  $1.5 \mu\text{M}$  against Raf.

#### 2.4.3. Geldanamycin-testosterone hybrids [304]

Working on similar lines, the same research group fused GDM with testosterone to selectively inhibit the androgen receptors. The stereochemistry of testosterone ( $17\beta$  hydroxyl) was maintained as for strong binding affinity of the steroid hormone. With this background, the series of GDM-testosterone linked hybrids (Fig. 52) were synthesised and evaluated for activity against prostate cancer cell lines. Structure activity relationship was established which revealed that hybrid 90 with 6-carbon alkynyl linker was most favorable with an  $IC_{50}$  of  $100 \text{ nM}$  compared to the GDM at  $40 \text{ nM}$  followed by 5-carbon alkynyl linker ( $IC_{50} = 200 \text{ nM}$ ). The most active hybrid molecule 90 exhibited strong and selective cytotoxicity towards prostate cancer cells expressing AR.

#### 2.4.4. Isothiocyanate-progesterone hybrids [305]

Isothiocyanates (ITC) constitute one of the important families of natural chemoprotective agents which can exert its anticancer effects by blocking initiation (through inhibition of Phase I enzymes that activates carcinogens) and by inducing Phase II enzymes that detoxify carcinogens and facilitate their excretion from the body. They can also down-regulate CYP3A4 transcription and enzyme activity in cultured human hepatocytes. Some naturally occurring isothiocyanates, sulforaphane (1-isothiocyanato-4-(methylsulfinyl)-butane) have received special attention due to its potent anticancer and chemoprotective property [306]. With this background and in view of the facilitation of internalization of the cytotoxic drugs by a steroid moiety [307–315], the authors

**Fig. 44.** Isatin-Thiazolidinone hybrid.

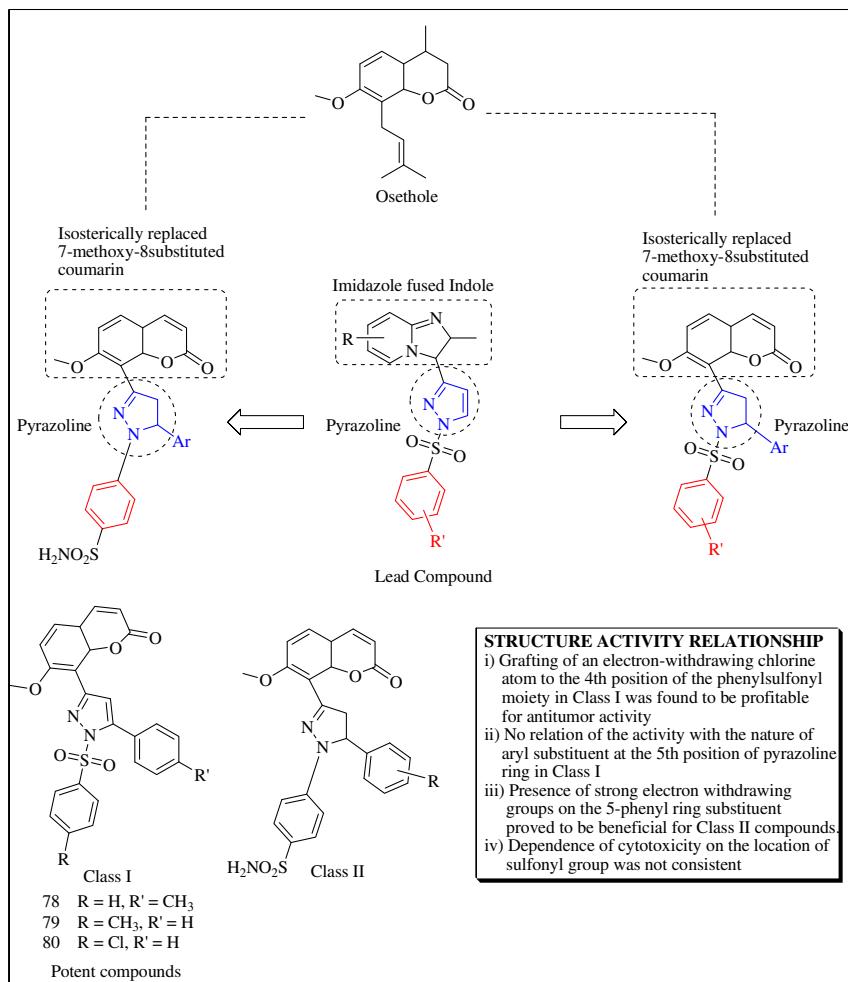


Fig. 45. Coumarin-pyrazoline hybrids.

synthesised new hybrid molecules of isothiocyanate and progesterone and their metal complex (Fig. 53). The hybrids were evaluated in a multiple panel of hormone-dependent (MCF-7, T47D), and hormone-independent (BT20 and MDA-MB231) breast cancer cell lines as well as androgen-independent prostate (PC3) cancer cell line by MTT assay. Hybrid 91 (copper complex) displayed highest cell growth inhibition. The highest apoptotic action was also shown by the copper complex, which was mediated through the inhibition of Akt signaling similar to the one shown by isothiocyanate compounds.

#### 2.4.5. Hybrid aza-steroid alkylators [316]

In view of encouraging results of hybrids employing azasteroids as biological carrier, Dimitrios T.P. Trafalis tested two alkylating homo-aza-steroid esters, lactandrate and lactestoxate (Fig. 54), for antineoplastic activity i.e. cytostatic and cytotoxic effects on nine human colon carcinoma cell lines. The *in vivo* anti-tumor effect was determined against two rodent colon carcinomas, the Colon 26 and the relatively chemoresistant Colon 38 carcinoma, as well as against the human xenograft CX-1 colon carcinoma.

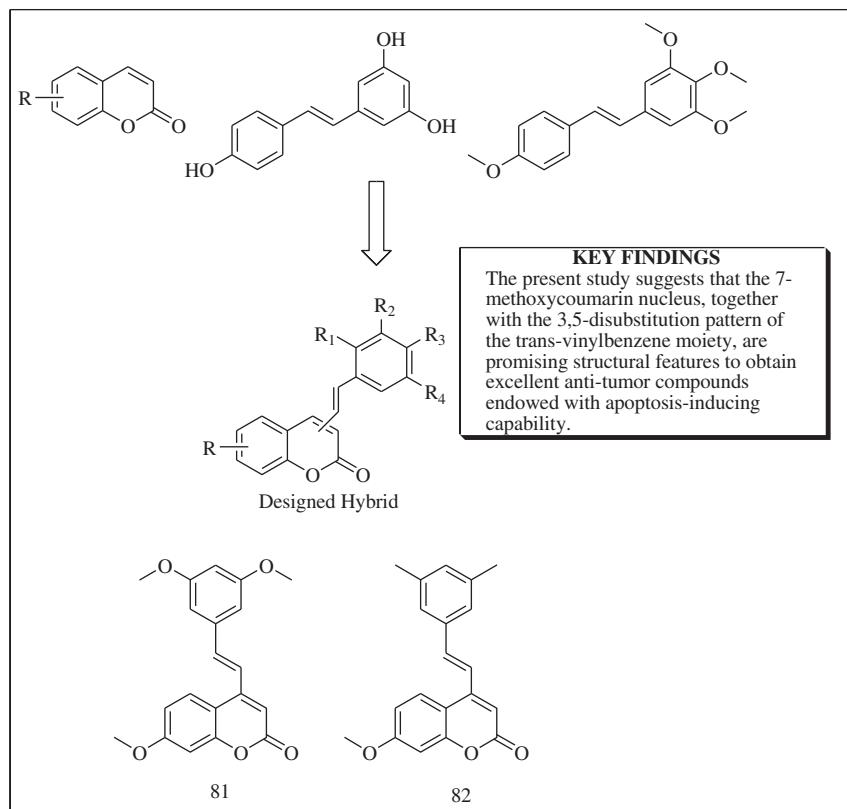
#### 2.4.6. Platinum based steroidal hybrids [317]

Platinum (II)-based anticancer therapies are considered to be an effective methodology for the treatment of cancer [318]. Platinum derivatives cisplatin, carboplatin, oxaliplatin, nedaplatin, iobaplatin, and heptaplatin are used in clinics [319–321]. These complexes

have been mainly used for the treatment of solid tumors, particularly small cell lung, ovarian, testicular, head, and neck tumors. The antitumor activity of platinum drugs is attributed to their interaction with DNA. Besides their remarkable antitumor potential, chemoresistance [322] and lack of selectivity [320] are the major drawbacks associated with these platinum based drugs. Kossi *et al.* examined the binding of a novel anticancer estradiol–platinum (II) hybrid molecule [323] (CD-37) (Fig. 55) with calf-thymus DNA *in vitro* and to compare the results with cisplatin drug which exerts its binding to DNA causing DNA bending and interfering with DNA replication and transcription. In the present study, solution containing various CD-37 or cisplatin concentrations were reacted with DNA at physiological pH. Spectroscopic techniques were used to characterize the drug binding mode, the binding constant, and structural variations of DNA in aqueous solution which exhibited that direct guanine and adenine N7 bindings for cisplatin drug, while indirect binding of CD-37 (H-bonding) is prevailed in the CD-37–DNA complexes. The stronger binding of cisplatin to DNA duplex over CD-37 exhibited major differences in their binding modes Both CD-37 and cisplatin drugs induced DNA aggregation at high drug concentration, which caused DNA structural changes.

#### 2.4.7. Estradiol-PEG-linked platinum (II) hybrid molecules [324]

Mandeville *et al.* designed 17 $\beta$ -estradiol-platinum (II) hybrid molecules (Fig. 56) linked through a polyethylene glycol (PEG) chain at position 16  $\alpha$  of the steroid nucleus and bear a 16 $\beta$ -

**Fig. 46.** Coumarin-stilbene hybrids.

hydroxymethyl side chain. The cytotoxicity of the 17 $\beta$ -estradiol-PEG-platinum (II) complexes was evaluated on MCF-7 (ER+) and MDA-MD-231 (ER-) breast cancer cell lines. Hybrid 94 displayed significant potential with IC<sub>50</sub> values = 2.18  $\mu\text{M}$  (MCF-7) and 2.16 (MDA-MD-231).

#### 2.4.8. Imidazole derived steroidal hybrids [325]

Aromatase, a cytochrome P450 enzyme that catalyzes the conversion of androgens into estrogens in the last step of estrogen biosynthesis [326] are utilized in the treatment of advanced estrogen-dependent tumors; such as breast cancer, endometrial cancer, prostatic hyperplasia [327,328]. The proved aromatase inhibitory potential of steroidal drug, exemestane and azole containing anastrozole [329,330] led to the design of a series of imidazolyl substituted 16E-arylidostenoidal hybrids (Fig. 57). These derivatives were synthesized and evaluated for aromatase inhibitory activity. The steroidal hybrids displayed moderate inhibition of the aromatase enzyme. Compound 95 (IC<sub>50</sub>: 4.4  $\mu\text{M}$ ) was found to be seven times more potent in comparison to standard drug aminoglutethimide.

#### 2.5. Pyrrolo [2,1-c] [1,4]-benzodiazepine hybrids

The pyrrolo [2,1-c] [1,4] benzodiazepines (PBDs) (Fig. 58) are a family of DNA interactive antitumor antibiotics derived from Streptomyces species [331]. The PBD class of compounds that include the naturally occurring anthramycin and DC-81 exerts its cytotoxic and antitumor effects through modification of DNA, which leads to inhibition of nucleic acid synthesis and production of excision-dependent single and double-strand breaks in cellular DNA [332,333]. These antibiotics have been proposed to covalently bond to N2 of guanine to form a neutral minor groove adduct

[334,335]. In recent years, a number of PBD based symmetrical and unsymmetrical DNA cross-linking agents have been designed and synthesized that exhibit significant DNA binding and anticancer activity [336]. Although PBDs have shown high antitumor activity, significant cardiotoxicity hampers their clinical applications [337]. Design of PBD conjugates by linking it to DNA interactive agents or other functionalities with a view to enhance the anticancer activity while decreasing side effects [338,339] is at present the area of focus.

#### 2.5.1. PBD Hybrids with polyaromatic planar ring systems [340]

DNA intercalating potential resulting in anticancer activity of polyaromatic hydrocarbons is basically attributed to the planar ring system [341]. Some polyaromatic hydrocarbons such as chrysene and pyrene derivatives such as (1-pyrenylmethyl) amino alcohol, 2-[(aryl methyl) amino]-1,3-propanediol have proved their antitumor potential in clinical studies [342]. Keeping this in view, Kamal *et al.* speculated that PBD hybrids with such planar polyaromatic system may exhibit potential antitumor effects and coupled PBD's with chrysene in 2003 and pyrene in 2004. Thus polycyclic aromatic ring chrysene was linked at C8 position of PBD ring system through an alkylamide spacer anticipating PBD coupling to highly lipophilic aromatic amines could result in selective interactions with cancer cells as a major affect in cell killing. Chrysene-linked pyrrolo-benzodiazepine hybrids were prepared (Fig. 59) and evaluated for *in vitro* cytotoxicity studies against a panel of cell lines. Hybrids 100 exhibited promising anticancer activity with LC<sub>50</sub> < 10  $\mu\text{M}$  potency against one non-small cell lung cancer (NCI-H226, 4.5  $\mu\text{M}$ ), one melanoma cancer (UACC-62, 4.07  $\mu\text{M}$ ) and one renal cancer (A498, 6.29  $\mu\text{M}$ ) in the 60-cell line panel. Hybrid 99 displayed moderate DNA binding affinity as it elevated the helix melting temperature of CT-DNA by a 2.8 °C after incubation for 18 h at 37 °C. The DNA

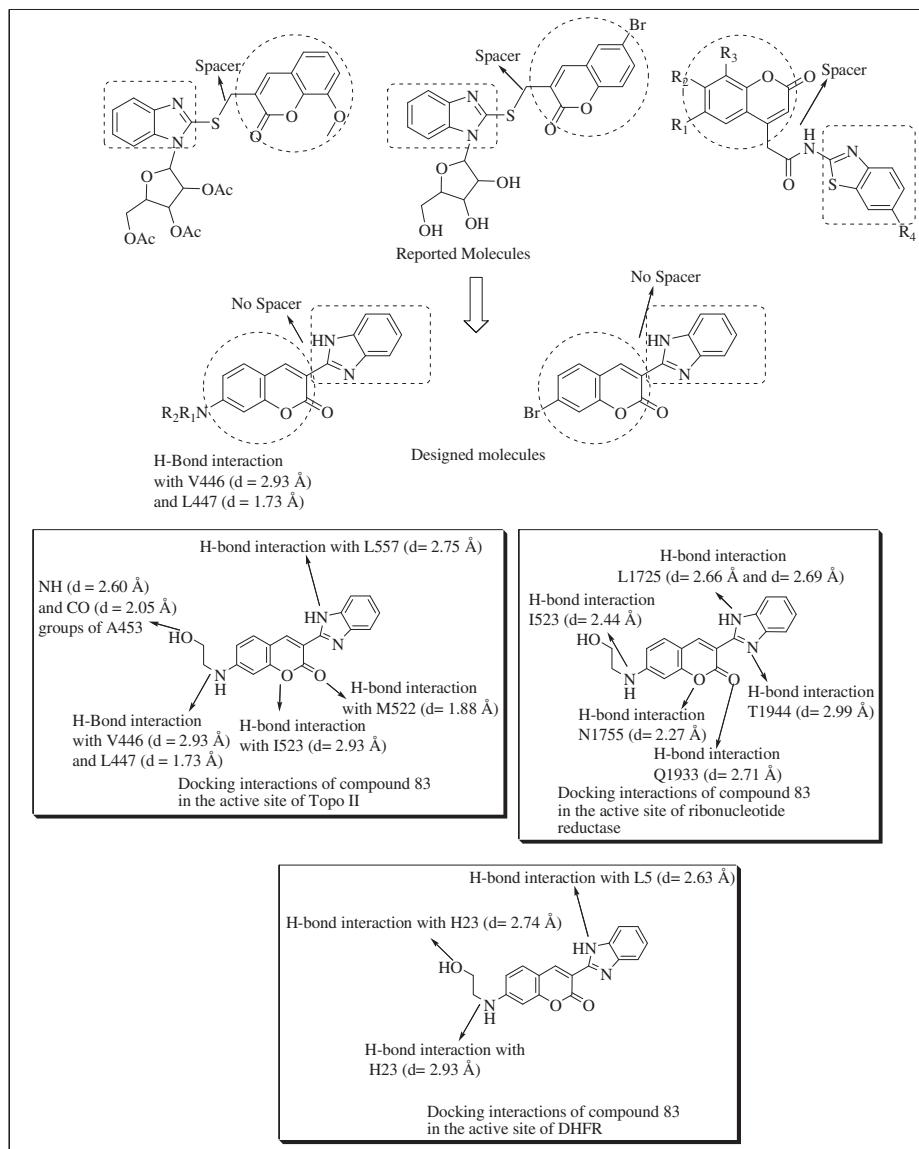


Fig. 47. Coumarin-benzimidazole hybrid.

binding activity for these novel chrysene was examined by thermal denaturation studies using calf thymus (CT) DNA.

In extension of their investigation, pyrene-linked pyrrolo-benzodiazepine hybrids (Fig. 60) were synthesised in 2004 [343] which exhibited potential anticancer activity in a number of human tumor cell lines. These hybrids exhibited remarkable DNA-binding ability in comparison to the parent pyrrolobenzodiazepine ring system (DC-81). Pyrene linked PBD 101 was found to be the most potent displaying LC<sub>50</sub> value ranging from 0.05 to 0.24 μM against various cell line employed for the *in vitro* cytotoxic studies and elevates the helix melting temperature of CT-DNA by a 6.5 °C. This increase of melting temperature was attributed to the additional effect of intercalation with DNA by the pyrene subunit apart from the covalent binding that may take place by the PBD ring system.

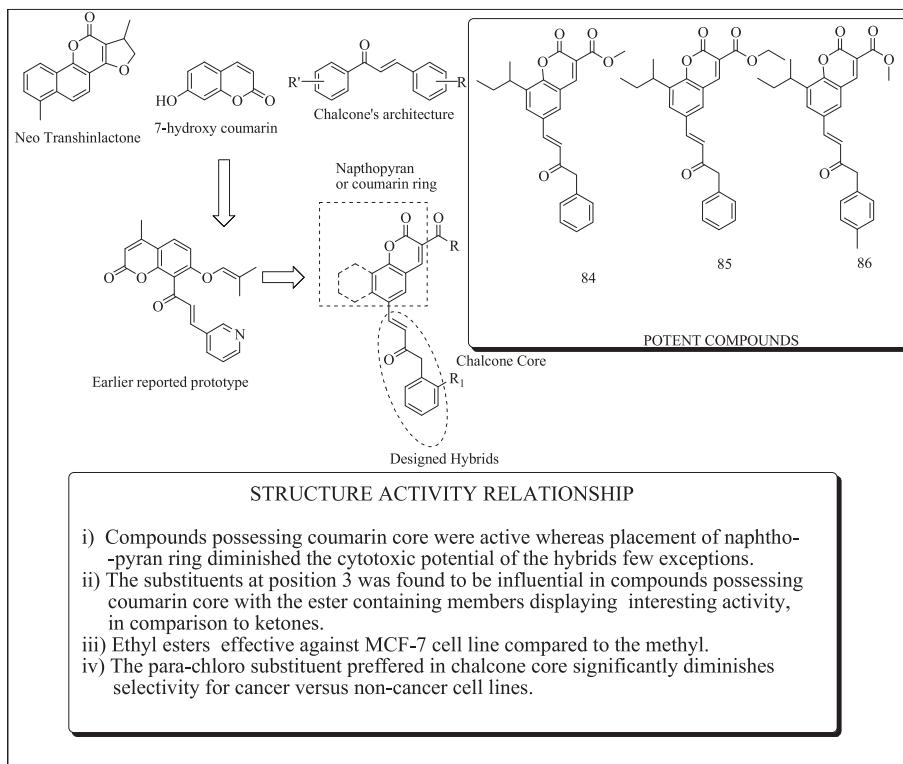
#### 2.5.2. Benzothiazoles and pyrrolo [2,1-c] [1,4] benzodiazepin-5-one [344]

Privileged structures Benzothiazoles have gained enough attention during the last decade due to their tumor cell killing potential [345,346]. Significant research on benzothiazoles led to

the recognition of DF 203 and 5F 203 (Phortess prodrug) [347] as novel anti-cancer drugs with unique mode of action. They are potent aryl hydrocarbon receptor binders in sensitive tumor cells leading to DNA damage by reactive intermediates generation through a sequence of complex processes. Keeping this in view, Bose *et al.* designed hybrids by fusing benzothiazole scaffold to DNA minor groove binders, PBDs (Fig. 61). The cytotoxic activity of the hybrids was evaluated *in vitro* against five tumor cell lines: THP-1 (human acute monocytic leukemia), U-937 (human histiocytic lymphoma), HL-60 (human promyelocytic leukemia), Jurkat (Human T-cell leukemia) and A-549 (lung carcinoma). Among the hybrids synthesised, 6 compounds showed significant cytotoxic activities. The fluoro analogue (hybrid 103) showed promising cytotoxic profile and specifically inhibited THP-1 cancer cell line (IC<sub>50</sub> = 0.49 μM).

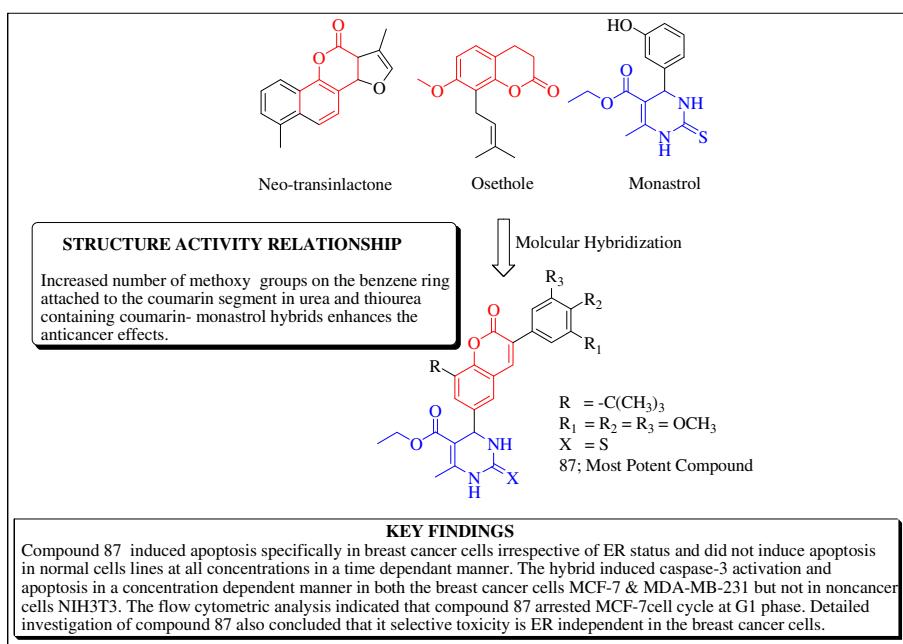
#### 2.5.3. Bisindole linked pyrrolo [2,1-c] [1,4] benzodiazepine conjugates [348]

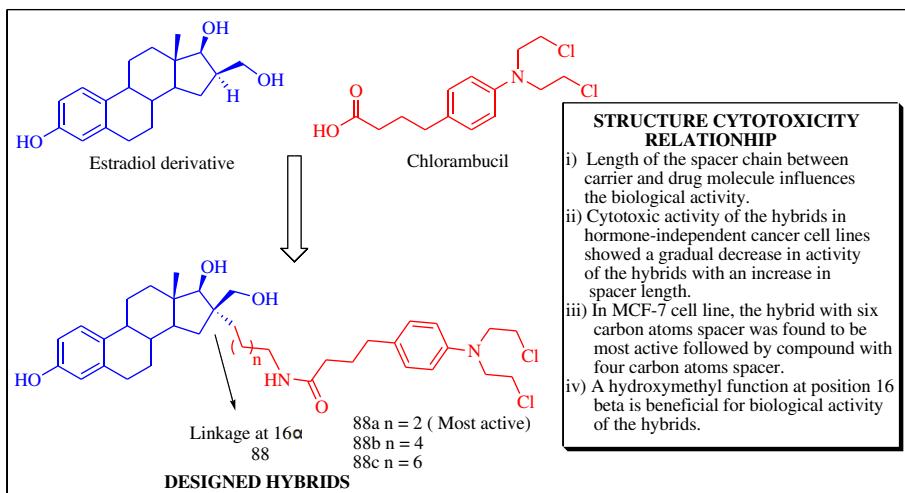
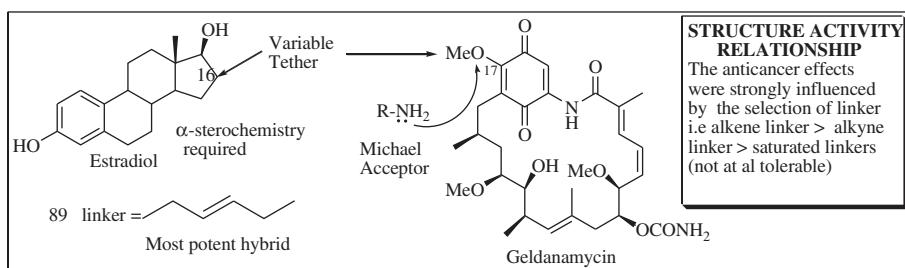
The potential of indolocarbazoles either of natural or synthetic origin as cyclin dependent kinases inhibitor and antiproliferating agent is well reported [349,350]. Bisindolyl methane (BIM) moiety

**Fig. 48.** Coumarin-chalcone hybrid.

linked hydroxamic acids and related compounds have proved their potential as HDAC inhibitors [351]. BIM was also identified as an active metabolite responsible for the anticancer effects of Indole-3-carbinol, a dietary component found predominantly in cruciferous vegetables [352]. Indole-3-carbinol is in phase I and II clinical trials for breast cancer prevention in the stomach by gastric juice [353]. With this background, a series of bisindole-pyrrolobenzodiazepine

conjugates (Fig. 62) linked through different alkane spacers was prepared and evaluated for their *in vitro* cytotoxicity and biological investigations of these conjugates on MCF-7 cell line in regulating HDACs as well as CDK inhibitor p21 were carried out. All compounds exhibited significant anticancer potency. The most potent compounds 104 and 105 ( $IC_{50}$  values of 0.19 and 0.14  $\mu\text{M}$ ) were investigated in detail on MCF-7 cell line.

**Fig. 49.** Coumarin-Manostrol hybrids.

**Fig. 50.** Estradiol-chlorambucil hybrids.**Fig. 51.** Geldanamycin-estradiol hybrid.

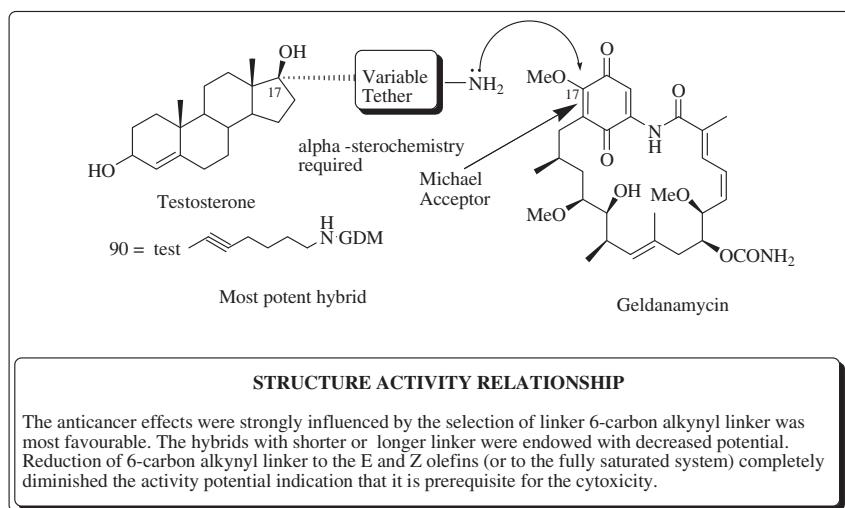
#### 2.5.4. PBD-indole conjugates [354]

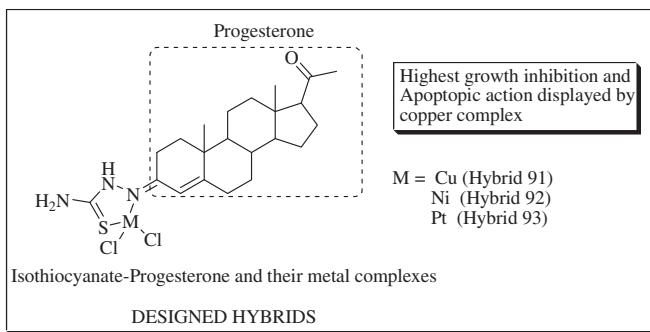
Promising anticancer profile displayed by DSB-120 [355–357] (a head-to-head linked tomaymycin dimer (DSB-120), CC-1065 [358], bizelesin [359], UTA-6026 [360] and K-252 [361] possessing an indole moiety in their chemical architecture led to the design of a series of novel pyrrolo [2,1-c] [1,4]benzodiazepine (PBD) hybrids (Fig. 63) by linking C-8 of DC-81 with an indole 2-carbonyl moiety through carbon chain linkers. Preliminary *in vivo* tests showed that these hybrid agents have potent antitumor/anticancer activity. The

hybrids were evaluated for cytotoxicity in human melanoma A2058 cells and were found effective as an antiproliferative agent than DC-81 and exhibited better DNA-binding ability. Among the hybrids, one of the promising hybrid 106 was tested to confirm whether its antiproliferative effect was associated with cell cycle progression.

#### 2.5.5. Anthranilamide-PBD conjugates [362]

The presence of anthranilamide moiety in some potent anti-tumor agents such as AAL-993 and CI-1040 [363,364] led to the

**Fig. 52.** Geldanamycin-testosterone hybrids.

**Fig. 53.** Isothiocyanate-progesterone hybrids.

synthesis of several derivatives, in particular piperazines to exploit their chemotherapeutic potential [365,366]. Kamal *et al.* in view of this designed anthranilamide fused PBD conjugates (Fig. 64) and evaluated their anticancer properties. All the hybrids showed potent activity with  $GI_{50}$  Values ranging from 0.13 to 29  $\mu\text{M}$  against a panel of human cancer cell lines selected from of lung, breast, oral, colon, cervix, ovary and prostate. Among the hybrids, hybrid 107, 108 and 109 were found to be most active with  $GI_{50}$  value ranging from 0.13 to 2.4  $\mu\text{M}$ . These three hybrids were further selected for cell cycle analysis in A375 human melanoma cancerous cell line. Activation of caspase -3 and apoptosis like enhancement in the levels of p-53 (considered as the master regulator of apoptosis) was observed with these hybrids.

#### 2.5.6. Naphthalimide –PBD hybrids [367]

The antitumor properties of Naphthalimides as DNA intercalating agents [368] resulted in the discovery of amonafide and mitonafide which are in clinical trials. Keeping in view the success of PBD based inhibitors [369–372] and in continuity of their research on PBD hybrids, Kamal *et al.* designed and synthesized C-8 linked naphthalimide–PBD hybrids (Fig. 65) with a view to have a combination of both the DNA-binding and intercalating properties in the same molecule. The linkers of varied length were utilized to probe the structural requirements for optimal *in vitro* anti-tumor activity. Hybrids 110 and 111 exhibited higher cytotoxic activity than the existing natural and synthetic pyrrolo [2,1-c]-[1,4] benzodiazepines. Hybrid 110 was more cytotoxic for colon ( $\text{Log LC}_{50} = -4.34 \text{ mol/L}$ ) and renal cancers ( $\text{Log LC}_{50} = -4.57 \text{ mol/L}$ ) with hybrid 111 for colon ( $\text{Log LC}_{50} = -4.41 \text{ mol/L}$ ) and melanoma cancers ( $\text{Log LC}_{50} = -4.43 \text{ mol/L}$ ).

#### 2.5.7. 2, 5-diaryloxadiazole-pyrrolobenzodiazepine [373]

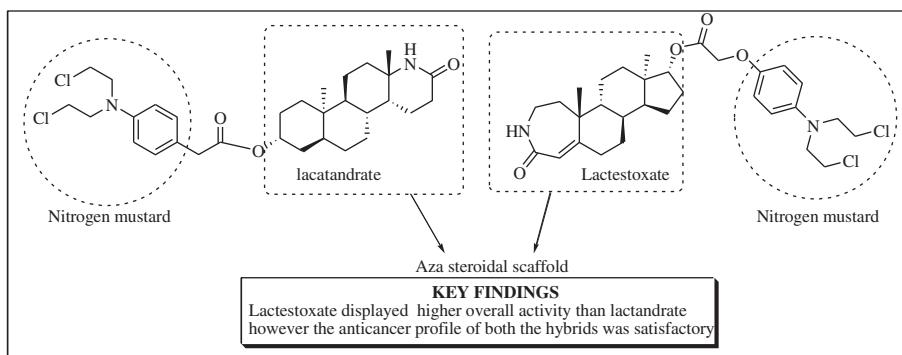
1, 3, 4-Oxadiazoles represents an important class of heterocyclic compounds [374] with diverse array of biological activities [375–

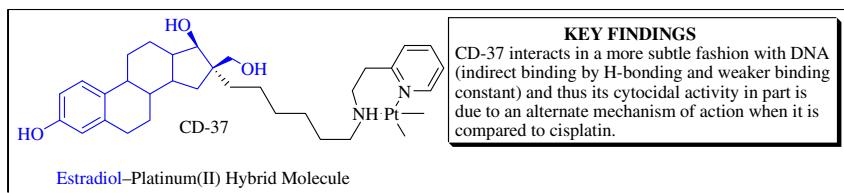
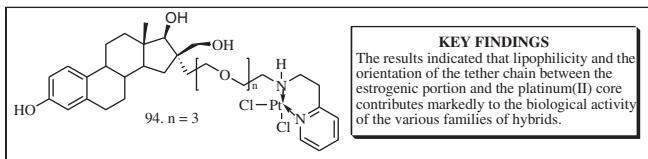
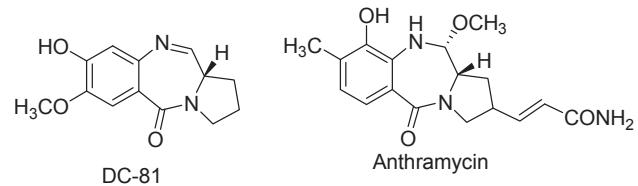
380]. The presence of toxophoric  $-\text{N}=\text{C}-\text{O}-$  linkage, reported bioisosterism with amide and ester functionalities and ability to participate in hydrogen bonding interactions with different receptors led to the inclusion of oxadiazoles in hybrid structure based design approach. Kamal *et al.* in 2010 designed PBD conjugates (Fig. 66) by linking a diaryloxadiazole moiety to the PBD (DC-81) scaffold through the stable alkane spacers. The synthesized hybrids were evaluated for their anticancer activity in a panel of human cancer cell lines of lung, breast, oral, colon, prostate, ovarian and cervix. These conjugates displayed promising activity with  $GI_{50}$  values ranging from  $<0.1$  to 0.29  $\mu\text{M}$ . The cell viability assay of the two most promising compounds 112 and 113 showed cytotoxicity in A375 cells at 4  $\mu\text{M}$  concentration.

## 2.6. Non-classified hybrids

### 2.6.1. Psorospermin/quinobenzoxazine hybrids [381]

Psorospermin (see Fig. 1A for structure) is a novel antitumor antibiotic isolated from the roots and stem-bark of the tropical African plant *Psorospermum febrifugum* [382,383], mechanistically related to another class of antitumor antibiotics, the ploramycins [384,385]. Psorospermin intercalates into the DNA helix, and the epoxide ring undergoes electrophilic attack by N7 of guanine [386]. It has been observed that alkylation reactivity of psorospermin with specific sequences is significantly increased in the presence of topoisomerase II [387]. Psorospermin leads to selective DNA alkylation of N7 of guanine within the topoisomerase II-DNA gate sites [387]. Quinobenzoxazine A-62176 is a fluoroquinolone analogue with anticancer properties [388–390]. Biochemical studies on A-62176 have indicated that a 2:2 drug- $\text{Mg}^{2+}$  dimer bind to DNA. Earlier it was reported that A-62176 competes with psorospermin within the topoisomerase II-DNA complex [391]. The mechanistic insights of Psorospermin and A-62176, the steric and electronic similarities between the two which indicated that they might overlap within the intercalation site in the duplex DNA and interact similarly with the topoisomerase II-DNA complex led to the design and synthesis of new DNA alkylation agents that form irreversible DNA adducts with the topoisomerase II-DNA complex. Molecular modeling studies of psorospermin and A-62176 within the complex indicated that the designed structures should have optimal  $\pi-\pi$  stacking interactions and alkylating properties. Thus the design strategy involved fusion of epoxydihydrofuran ring of psorospermin as a DNA alkylating moiety to the pyridobenzophenoxazine ring of A-62176 (Fig. 67). Enhanced DNA alkylating activity in the presence of topoisomerase II, significant activity against all the cancer cells tested at submicromolar concentrations were observed for the hybrids. The results confirmed that planar nature of both molecules and their reactive epoxide moieties are required for optimum activity. Hybrid 114 displayed

**Fig. 54.** Hybrid aza-steroid alkylators.

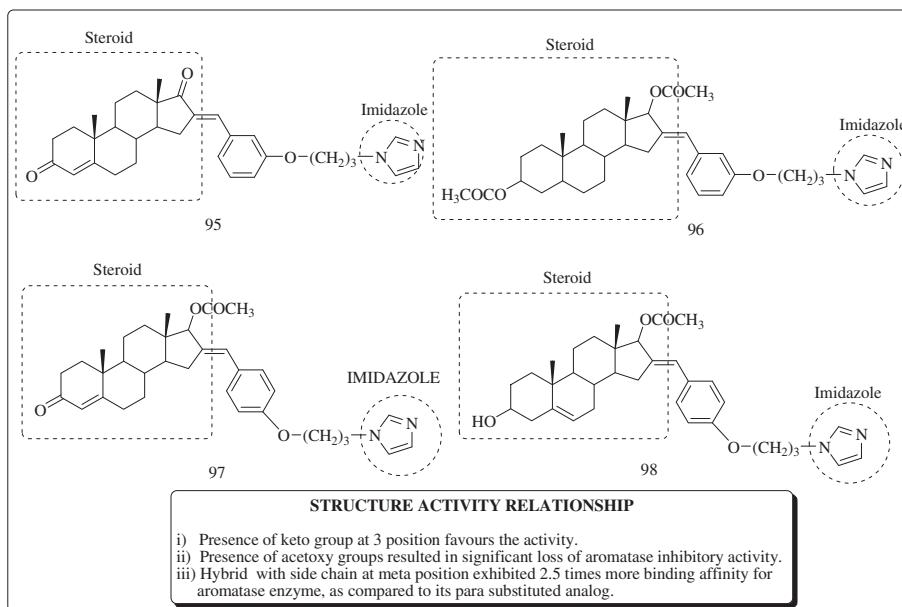
**Fig. 55.** Platinum based steroidal hybrids.**Fig. 56.** Estradiol-PEG-linked platinum (II) hybrid.**Fig. 58.** Pyrrolo [2,1-c] [1,4] - benzodiazepines.

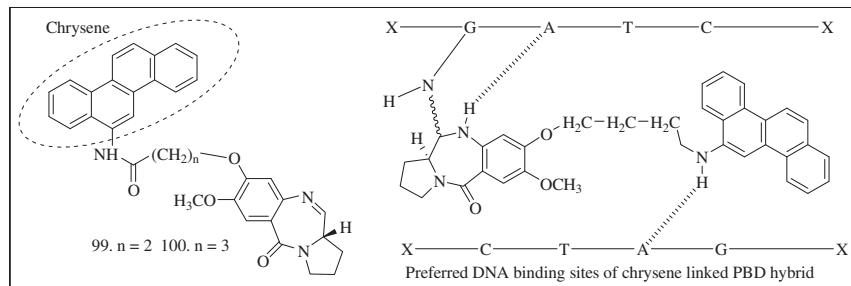
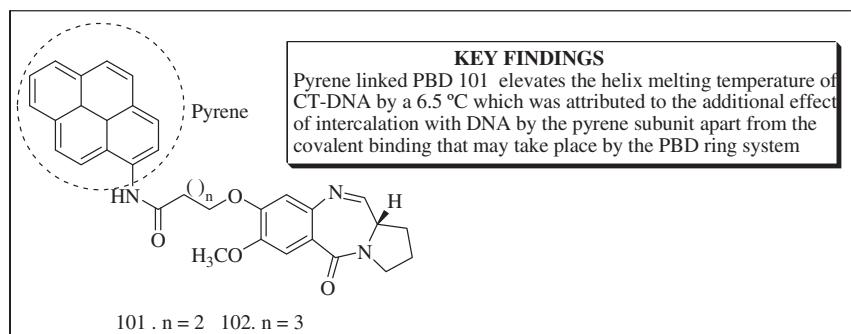
stable binding with duplex DNA, and its reactive epoxide moiety was found to be close to the nucleophilic N7 of guanine, resulting in stronger DNA alkylating activity than psorospermin in the presence of topo-isomerase II. Hybrid 115 which was designed modifying the functional epoxy group with chlorohydrin, with the aim of enhancing both nucleophilicity and accessibility to N7 of guanine showed more potent cytotoxicity than hybrid 114 against various cancer cell lines. Hybrid 115 displayed significant cytotoxicity against various cell lines employed with IC<sub>50</sub> values ranging from 0.002 to 0.13 μM and was found to be most active against Granta (lymphoma) cell line.

#### 2.6.2. Norindenoisoquinoline-camptothecin hybrids [392]

DNA topoisomerase I (Top1) has become an important target for the design of novel antitumor drugs [393]. Camptothecin is one of the most explored top 1 inhibitor; however it suffers from poor water solubility, high toxicity, and metabolic instability [394]. These drawbacks led to the development of the two clinically useful water-soluble CPT derivatives topotecan (2) and irinotecan but

were associated with some limitations such as reversible drug interaction and opening of Ring E to hydroxy carboxylate [395–402]. Several indenoisoquinoline and indolocarbazoles compounds such as NSC314622, indimitecan (NSC 725776) and indotecan (NSC 724998) have been reported as TOP1 inhibitors [403–406]. Fox *et al.* in view of these reports designed Indenoisoquinoline-Camptothecin Hybrids via two strategies (Fig. 68). One involved the synthesis of target hybrids that closely resemble camptothecin as per the proposed structural analogy such as the lactam of the lead Indenoisoquinoline would correspond to the lactam of camptothecin while the second strategy involved placement of various alkenyl substituents to the C-11 position of the indenoisoquinolines which were assumed to project into the DNA minor groove. The hybrids were evaluated for cytotoxicity in human cancer cell cultures as well as for activity vs. top1. These hybrids proved to be less cytotoxic and displayed less activity against top1. Hybrid 116 with a 3'-aminoalkenyl substituent at the C-11 position of the indenoisoquinoline system was significantly more potent than the indenoisoquinoline in both assays. The hybrid

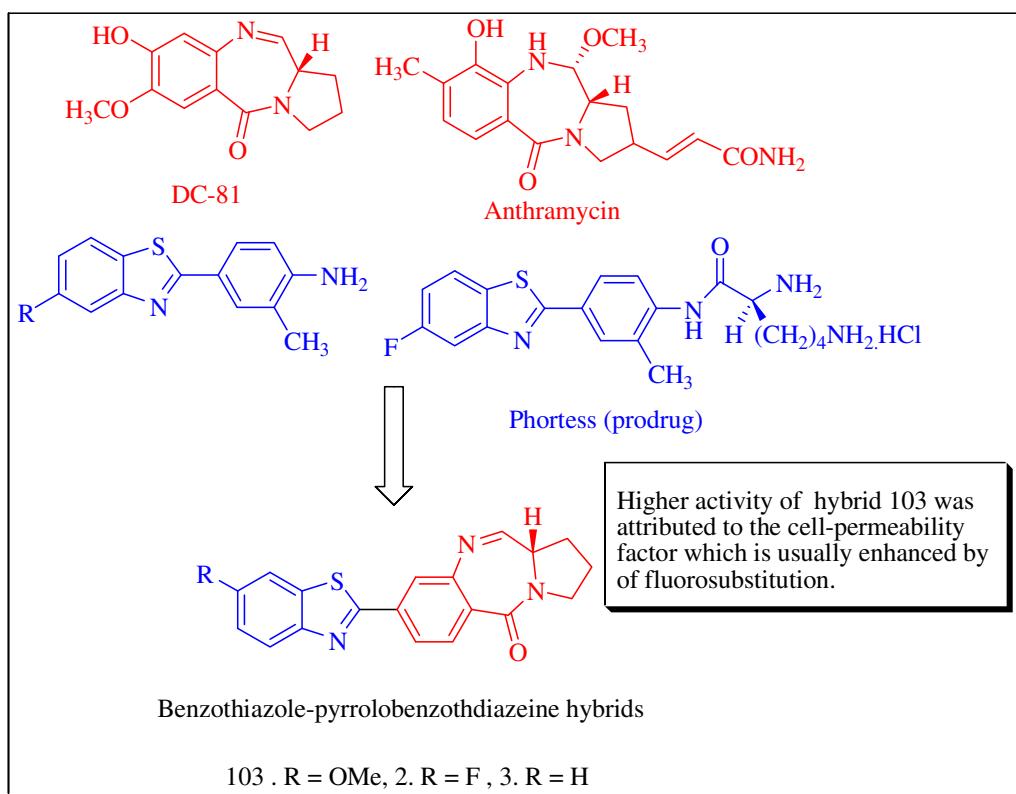
**Fig. 57.** Imidazole derived steroidal hybrids.

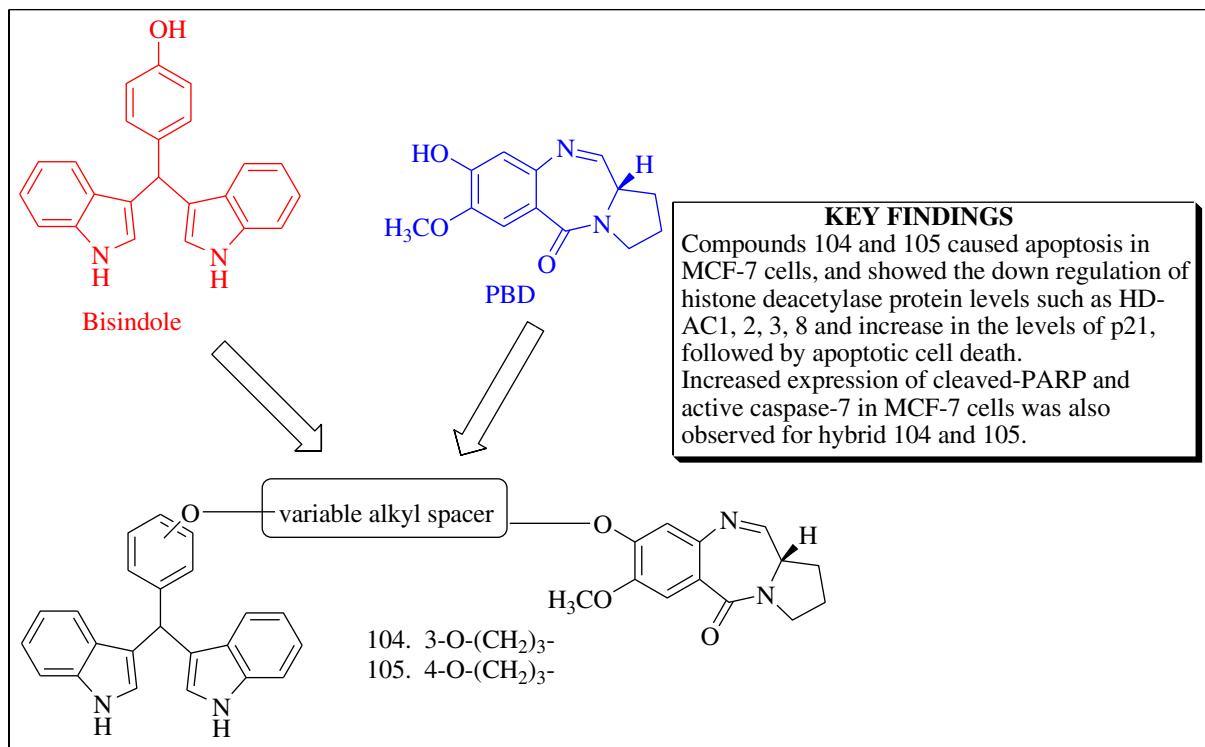
**Fig. 59.** PBD hybrids with polyaromatic planar ring systems.**Fig. 60.** PBD hybrids with polyaromatic planar ring systems.

displayed significant cytotoxicity with an IC<sub>50</sub> range of 0.028–1.8 μM against various cell lines. These results indicated that C-11 aminoalkyl substituents that were assumed to project into the minor groove enhanced the cytotoxicity and top1 inhibitory activity of the parent indenoisoquinoline system.

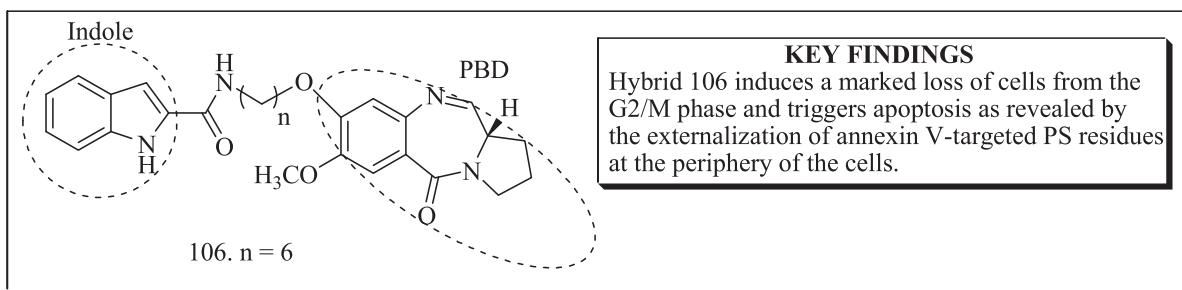
#### 2.6.3. Piperazinyl benzothiazole/benzoxazole-1, 3, 4-oxadiazole-2-thiol hybrids [407]

The anticancer potential of derivatives with piperazine ring linked to a terminal fragment usually containing an amide or imide function have been well explored. Reports of arylpiperazinyl

**Fig. 61.** Benzothiazoles and pyrrolo [2,1-c] [1,4] benzodiazepine-5-one.



**Fig. 62.** Bisindole linked pyrrolo [2,1-c] [1,4] benzodiazepine conjugates.



**Fig. 63.** PBD-INDOLE conjugates.

alkylthio benzoheterocycles as selective 5-HT1A serotonin receptor ligands [408] and pyridazin-3(2H)-one derivative linked with piperazine nucleus with a three carbon spacer endowed with significant inhibitory potential against HeLa (Cervical) cell lines [409,410]. The presence of benzothiazoles and oxadiazoles in number of recently reported anticancer agents [411], some of them even displaying potential in clinical studies tempted the authors to synthesize hybrids incorporating piperazine, benzothiazole/benzoxazoles and 1,3,4-oxadiazole heterocyclic ring systems in a single molecule using a three carbon spacer (Fig. 69). The hybrids were tested for *in vitro* antiproliferative activity against five cell lines, viz. MCF-7 (Breast), HeLa (Cervical), HepG2 (Liver), A431 (Skin) and A549 (Lung). Among the synthesised hybrids, hybrid 117 displayed the highest activity in A431 ( $IC_{50} = 36.9 \mu\text{M}$ ) and hybrid 118 showed most potent activity among the synthesized compounds in MCF-7 cell line ( $IC_{50} = 39 \mu\text{M}$ ).

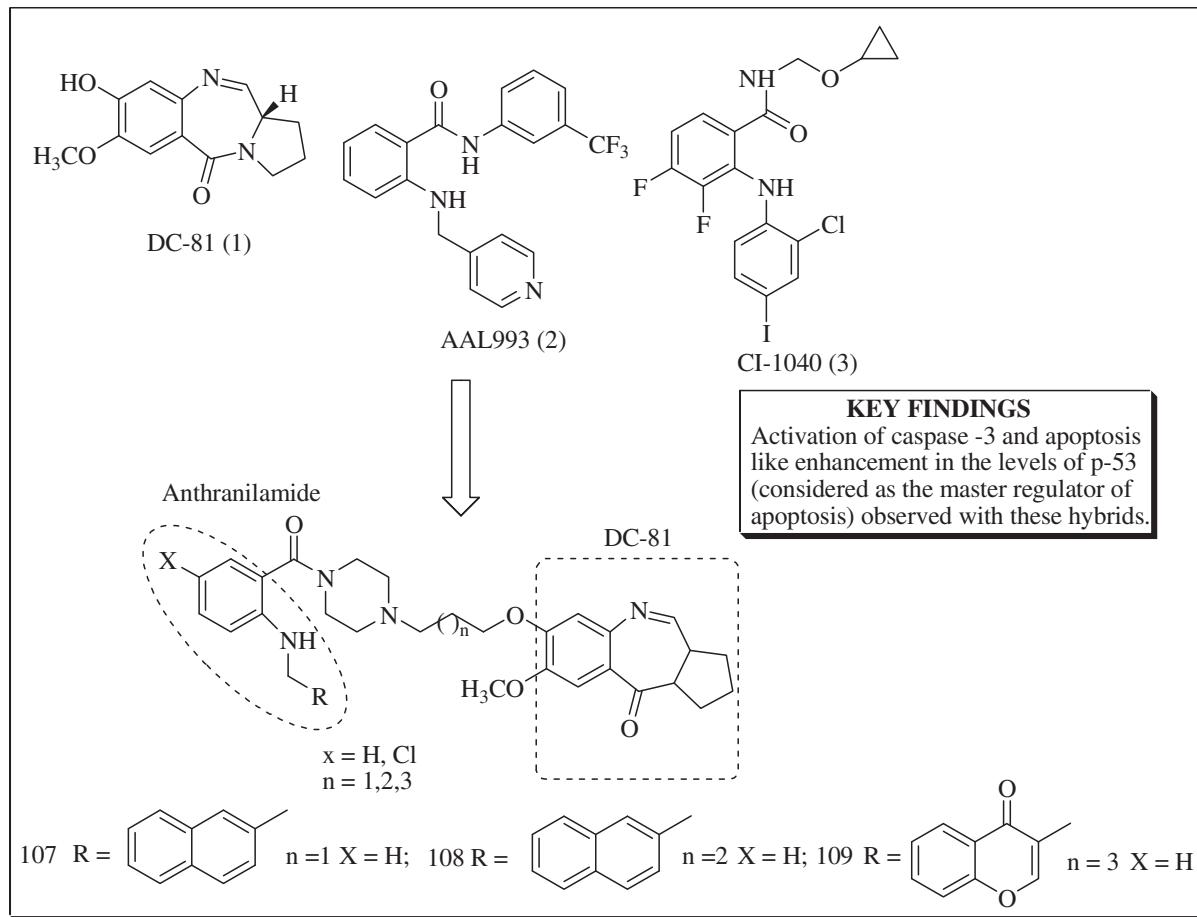
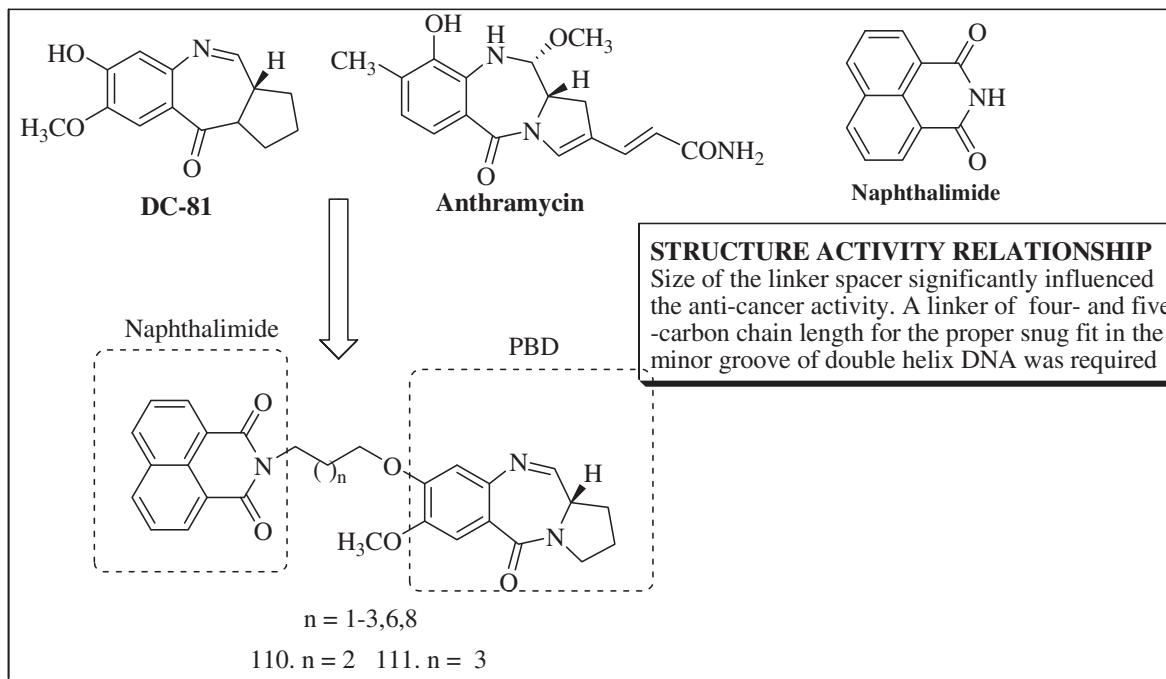
#### 2.6.4. Tyrosine–Chlorambucil hybrid [412]

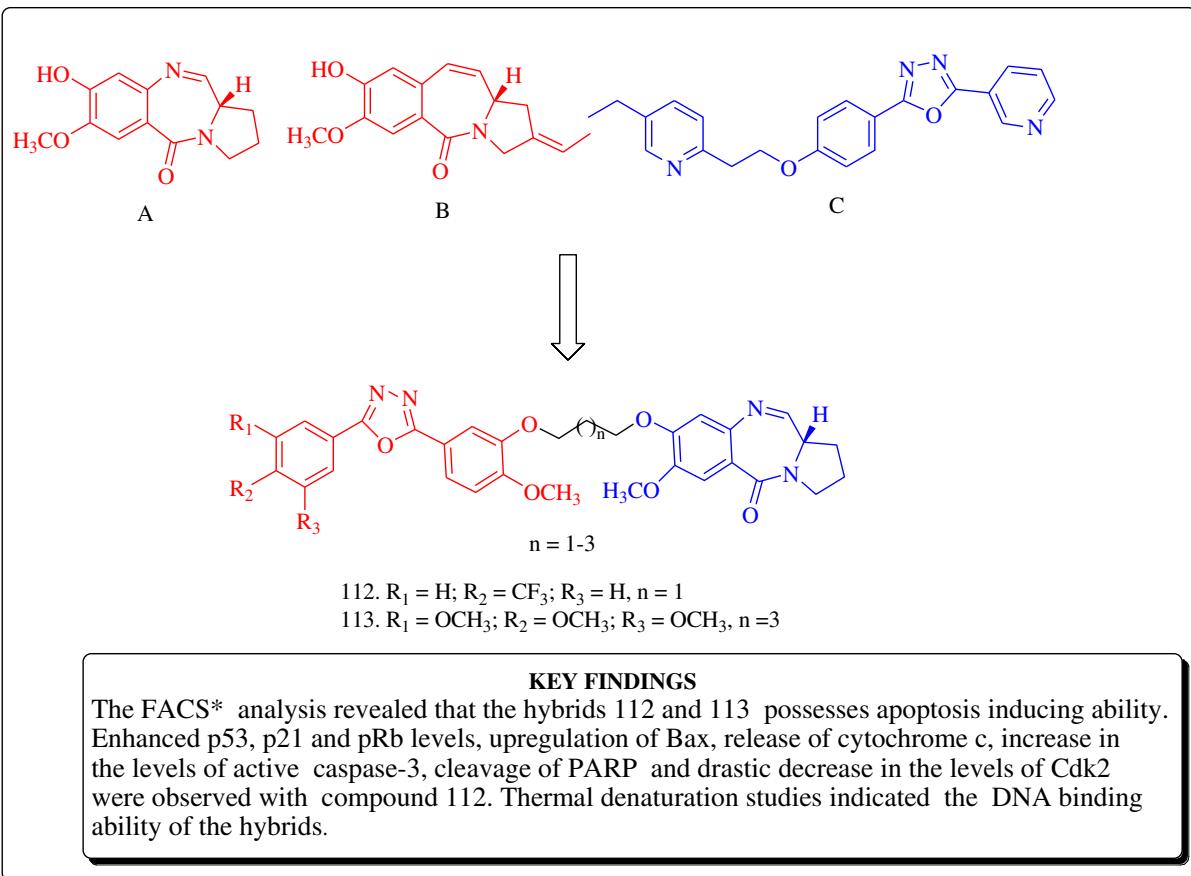
Estrogen receptor  $\alpha$  is a nuclear protein, which is present in breast cancer cells and becomes over-expressed in cancerous cells [413,414]. In search of molecules with potential to kill the breast

cancer cell, Teaux *et al.* designed tyrosine–Chlorambucil hybrid utilizing the amino acid tyrosine as the biological carrier for the cytotoxic drug (Fig. 70). Tyrosine was employed as carrier in view of structural resemblance of tyrosine with estradiol and was speculated to possibly mimic the natural hormone. Thus tyrosine was selected to act as an estrogenic ligand. Ortho, meta and para-tyrosine–chlorambucil analogs were synthesized in order to generate new anticancer drugs with structural diversity, more specifically in regard to the phenol group location. The cytotoxicity of the tyrosine–chlorambucil regioisomers was evaluated on MCF-7 (ER+) and MDA-MD-231 (ER-) breast cancer cell lines. All the hybrids were more effective than the parent drug, chlorambucil. Hybrid 119 with the phenol group located in meta position, showed the most significant cytoidal activity [7.36 times more active than chlorambucil] with  $IC_{50} = 17.72 \mu\text{M}$  on estrogen receptor positive (ER+) MCF-7 breast cancer cell lines and  $32.24 \mu\text{M}$  (ER-) on MDA-MB-231 breast cancer cell lines.

#### 2.6.5. Platinum–acridine hybrids [415]

Platinum–acridine agents have shown excellent activity in solid tumors resistant in comparison to cisplatin, particularly against

**Fig. 64.** Anthranilamide-PBD conjugates.**Fig. 65.** Naphthalimide-PBD hybrids.



\*Fluorescence-activated cell sorting

**Fig. 66.** 2,5-diaryloxadiazole-pyrrolobenzodiazepine.

NSCLC cell lines [416] and were found to be an efficient inhibitor of DNA replication and inducer of cell death [417]. In view of the dose-limiting toxicity associated with these platinum-acridine hybrids [418] and in an attempt to explore platinum-acridines as cytotoxic “warheads” attached to tumor-directed carriers using chemically or enzymatically reversible linkers in receptor-targeted therapies, Graham *et al.* designed platinum-acridine hybrids agents (Fig. 71) containing carboxylic acid ester groups. The goal of the study was to generate a suitable precursor molecule by installing a carboxylic acid ester group at the amidine moiety of the acridine carrier ligand that can be converted into a carboxylate chelate anticipating incorporation of the carboxylato ligand as a pendant group into a chelate, similar to the dicarboxylato leaving group in the clinical drug carboplatin, to produce a more stable, yet DNA reactive entity. The platinum-acridines were evaluated for cytotoxicity against NSCLC (NCI-H460), ovarian (OVCAR-3), breast (MDA-MB-231, MCF-7) and pancreatic (PANC-1) cancer cell lines and majority of the platinum-acridines displayed significantly cytotoxicity better than cisplatin. The most active derivatives and the unmodified parent compounds showed up to 6-fold higher activity in ovarian cancer (OVCAR-3) and breast cancer (MCF-7, MDA-MB-231) cell lines than cisplatin. Hybrid 120 inhibited the cell proliferation at nanomolar concentrations in pancreatic (PANC-1) and non small cell lung cancer cells (NSCLC, NCI-H460) with IC<sub>50</sub> value of 11 and 86 nM respectively. It was further demonstrated with the aid of high-performance liquid chromatography and electrospray mass spectrometry (LC-ESMS) that the ester moieties undergo platinum-mediated hydrolysis in a chloride concentration-dependent manner to form carboxylate chelates.

#### 2.6.6. Novel arylsulfoanilide–oxindole hybrid [419]

The anticancer effects of clotrimazole (CLT), eicosapentaenoic acid (EPA), and troglitazone are triggered by the partial depletion of intracellular Ca<sup>2+</sup> stores which activates eIF2 kinases (PKR and/or PERK), resulting in phosphorylation of eIF2α on serine 51 leading to its inactivation which in turn inhibits primarily ternary-complex-dependent translation initiation [420–422]. Translation initiation plays a vital role in the expression of oncogenic, prometastatic, and growth regulatory proteins and inhibitors of translation initiation constitutes an potent class of anticancer agents [423]. The translational initiation inhibitory potential of 3, 3-diaryloxindole and several sulfonamide, in particular E7070 (a para substituted diaryl sulfonamide presently in clinical trials) [424–426] led to the design of novel arylsulfoanilide-oxindole hybrids (Fig. 72). Natarajan *et al.* synthesised a series of arylsulfoanilide for the identification of key substitution patterns necessary for partial depletion of intracellular Ca<sup>2+</sup> stores mediated growth inhibition. The structure activity relationship for the synthesised sulfoanilides revealed that i) Both electron-donating and -withdrawing groups at the p-position results in enhanced growth inhibition and partial depletion of intracellular Ca<sup>2+</sup> stores ii) 4-position substituted with a hydrophobic group results in better depletion of intracellular Ca<sup>2+</sup> stores and growth inhibitory activity. iii). substituting the nitrogen of the sulfonanilide group resulted in decreased potential which suggested that the –NH of sulfonamide group is critical for its biological activity. iv). doubly substituting the aryl amino ring with an o-or m-hydroxy and p-methyl groups while maintaining the p-tert-butyl substitution on the aryl-sulfonyl ring enhances the activity. The authors incorporated these structural features of the potent

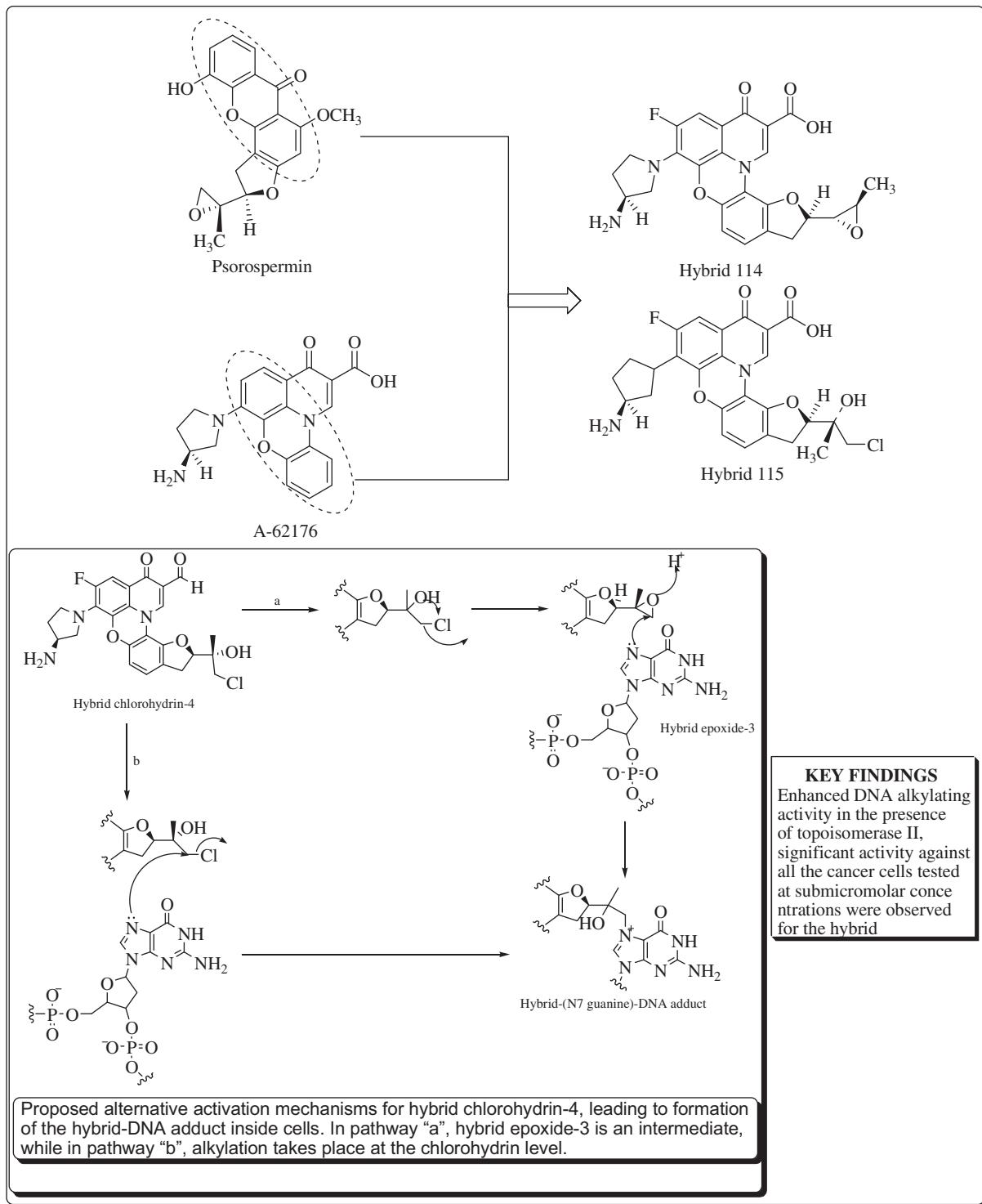


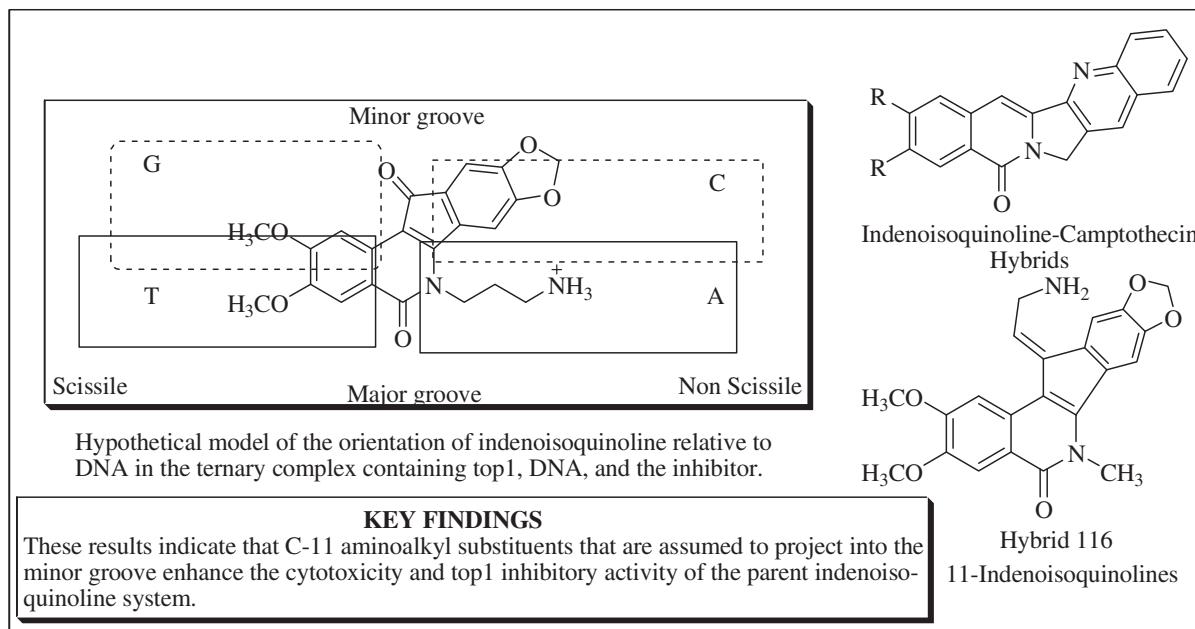
Fig. 67. Topoisomerase inhibitors based hybrids.

arylsulfoanilides into the diaryloxindole scaffold which resulted in a potent arylsulfoanilide-oxindole hybrid 121. Hybrid 121 inhibits cancer cell growth by partial depletion of intracellular  $\text{Ca}^{2+}$  stores and phosphorylation of eIF2R. Hybrid 121 displayed  $\text{GI}_{50}$  2.14  $\mu\text{M}$  against eIF2 $\alpha$ -P 4, 0.7  $\mu\text{M}$  against A549 and 1.08  $\mu\text{M}$  against DU145.

#### 2.6.7. Indole-barbituric acid hybrids [427]

Medicinal attributes of indole (core structural unit of indomethacin) and barbituric acid (core structural unit of fluorouracil)

in particular anticancer [428–431] tempted the research group lead by palwinder singh to fuse these molecular entities through carbon–carbon bond formation (Fig. 73). The hybrids were synthesised and evaluated against 60 cell line panel of human cancer cell. Among the hybrids, hybrids 122 and 123 were found to be the most cytotoxic with hybrid 122 exhibiting  $\text{GI}_{50}$  of 0.3  $\mu\text{M}$  for NCI-H460, 0.48  $\mu\text{M}$  for IGROV1, 0.3  $\mu\text{M}$  for OVCAR-5, 0.03  $\mu\text{M}$  for A498 and 0.1  $\mu\text{M}$  for MDA-MB-468 cell lines of NSCLC, ovarian cancer, renal cancer and breast cancer, respectively and hybrid 123  $\text{GI}_{50}$



**Fig. 68.** Norindenoisoquinoline-Camptothecin hybrids.

0.06  $\mu\text{M}$ , 0.1  $\mu\text{M}$ , 0.2  $\mu\text{M}$  and 0.02  $\mu\text{M}$  for IGROV1, OVCAR-5, A498 and MDA-MB-468 cell lines. Both the hybrids were docked in to the active site of COX-2 and thymidylate synthetase. Hybrid in the active site of COX-2 were stabilized by hydrogen bonding interactions between NH, CO of pyrimidine moiety and S353, Q192, H90 amino acid residues of the active site and hydrophobic interaction of the indole ring with W387 and Y385 residues. Suitable accommodation of the hybrids 122 and 123 in the active site clearly indicated their indomethacin like action. Docking study of these hybrids in the active site of thymidylate synthase and ribonucleotide reductase (enzyme involved in propagation of cancer) justified their accommodation by number of hydrogen bonding interaction. Lipinski values confirmed the drug like properties of these hybrids.

#### 2.6.8. Tyrosine – nitrogen hybrid molecules [432]

In view of success of estradiol linked anticancer molecule [433–435], Descoteaux *et al.* designed carrier ligand based anti-cancer hybrids employing tyrosine as the carrier (Fig. 74) in view of the fact that the binding cavity of ER- $\alpha$  can accommodate non steroid ligands provided it must possess the following characteristics : i) phenol ring similar to the A-ring of estradiol [436] ii) two polar functional groups, such as hydroxyl, must be present with appropriate interatomic distance [437] as in estradiol. However tyrosine due to its small size, does not fully occupy the ER- $\alpha$  binding cavity [438]. Thus the L-para-tyrosine was modified to get a structure similar to the steroid backbone by linking to ortho, meta and para-hydroxyaniline via an amide bonding. Chlorambucil was linked directly or via a carbon atom spacer (5 carbon or 10 carbon atoms) to get the desired hybrids. The hybrids were evaluated for their anticancer efficacy in hormone-dependent and hormone-independent (ER+; MCF-7 and ER; MDA-MB-231) breast cancer cell lines.

#### 2.6.9. Benzo [4,5]imidazo[1,2-d] [1,2,4]thiadiazole – $\alpha$ -bromoacryloyl hybrid [439]

Benzo [4,5]imidazo [1,2-d] [1,2,4]thiadiazoles ([1,2,4]BTHDs) as inhibitors targeting cysteine residue of biomolecules [440] have

been recently reported. The proposed enzymatic mechanism of these molecules involves the nucleophilic attack of the active site cysteine thiol at the sulfur atom leading to the formation of an S–S bond with N–S ring opening [441]. However lack of reactivity towards other nucleophiles such as amines and alcohols [442] suggested that an appropriate C-3 substituent in the tricyclic [1, 2, and 4] BTHD can enhance both enzyme affinity and reactivity [443]. The presence of  $\alpha$ -bromoacryloyl alkylating moiety in pyrroloiminoquinone cytotoxic alkaloids Discorhabdin A [444], Discorhabdin G [445] and distamycin-like minor groove binders for example, PNU-166196 (currently in phase II clinical trials) [446] whose reactivity has been assumed to be based on a first-step Michael-type nucleophilic attack followed by a further reaction of the bromo substituent  $\alpha$  to the carbonyl, leading to a second nucleophilic substitution or to beta elimination. In view of thiol trapping ability of Benzo [4,5] imidazo [1,2-d] [1,2,4]thiadiazoles ([1,2,4]BTHDs) and  $\alpha$ -bromoacryloyl moieties, Romagnoli *et al.* designed conjugates incorporating both the functionalities (Fig. 75). The hybrids were evaluated for cytotoxic activities against the human myeloid leukemia HL-60 and U937 cell lines and human melanoma SK-MEL-1 cells. Hybrids 124 and 125, with N-unsubstituted indole, were the most active. Hybrid 124 exhibited an IC<sub>50</sub> value ( $\mu\text{M}$ ) of  $0.29 \pm 0.03$ ,  $0.24 \pm 0.03$ ,  $2.09 \pm 0.39$  against HL-60, U937 and SK-MEL-1 and hybrid 125 exhibited an IC<sub>50</sub> value ( $\mu\text{M}$ ) of  $0.55 \pm 0.18$ ,  $0.40 \pm 0.11$ ,  $3.02 \pm 0.62$  against HL-60, U937 and SK-MEL-1.

#### 2.6.10. 2-phenylbenzofuran-imidazole hybrids [447]

Anticancer potential of naturally occurring benzofurans such as ebenfuran III [448] and moracins [449] and antitumor activities of imidazolium salts, especially imidazolium halides [450], Lepidiline A and Lepidiline B, isolated from the roots of *Lepidium meyenii*, against various human cancer cell lines [451] led to the design of novel hybrid compounds of imidazole -benzofurans (Fig. 76). The hybrids were evaluated for cytotoxicity against myeloid liver carcinoma (SMMC-7721), colon carcinoma (SW480), breast carcinoma (MCF-7), lung carcinoma (A549) and leukemia (HL-60) cell lines. Hybrid 129 with a naphthylacyl substituent at position-3 of imidazole was found to be the most potent derivative against all human

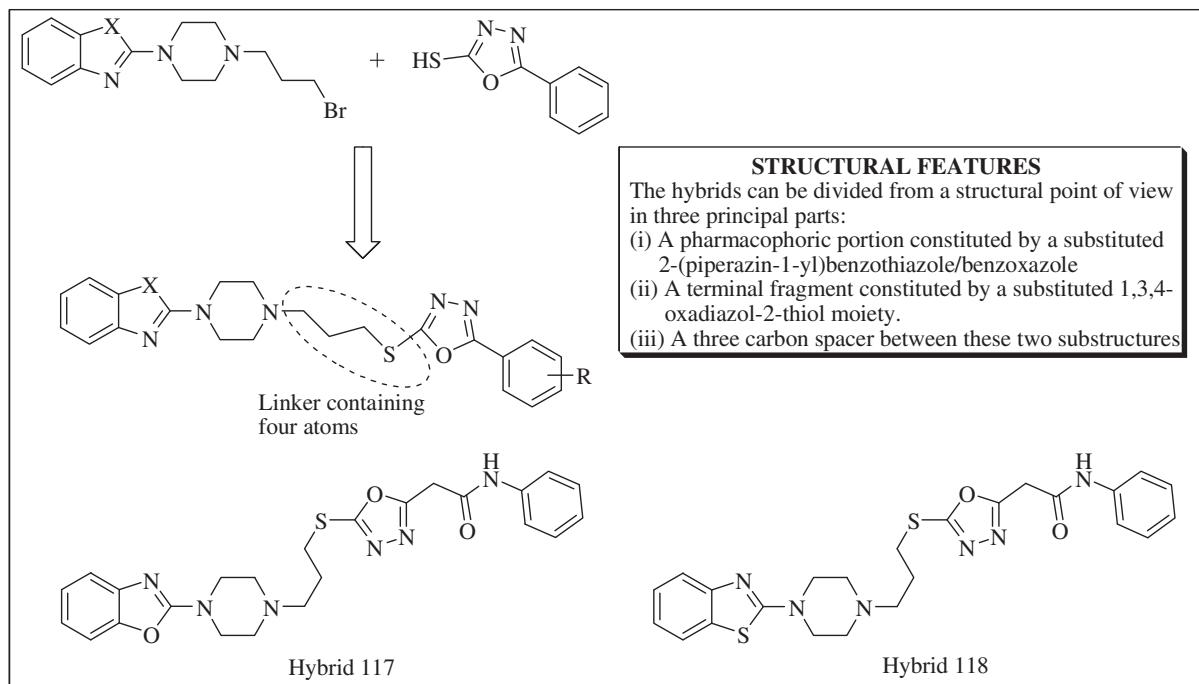


Fig. 69. Piperazinyl benzothiazole/benzoxazole-1, 3, 4-oxadiazole-2-thiol hybrids.

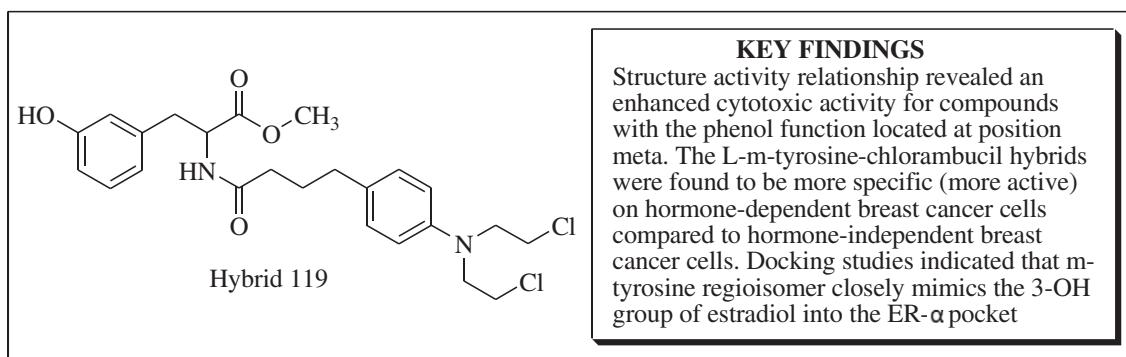


Fig. 70. Tyrosine-chlorambucil hybrid.

cell lines displaying most potent activity against liver carcinoma (SMMC-7721) with  $IC_{50}$  value ( $1.65 \mu M$ ) 5.4-fold more sensitive to DDP (Cisplatin) ( $IC_{50} = 1.65 \mu M$ ).

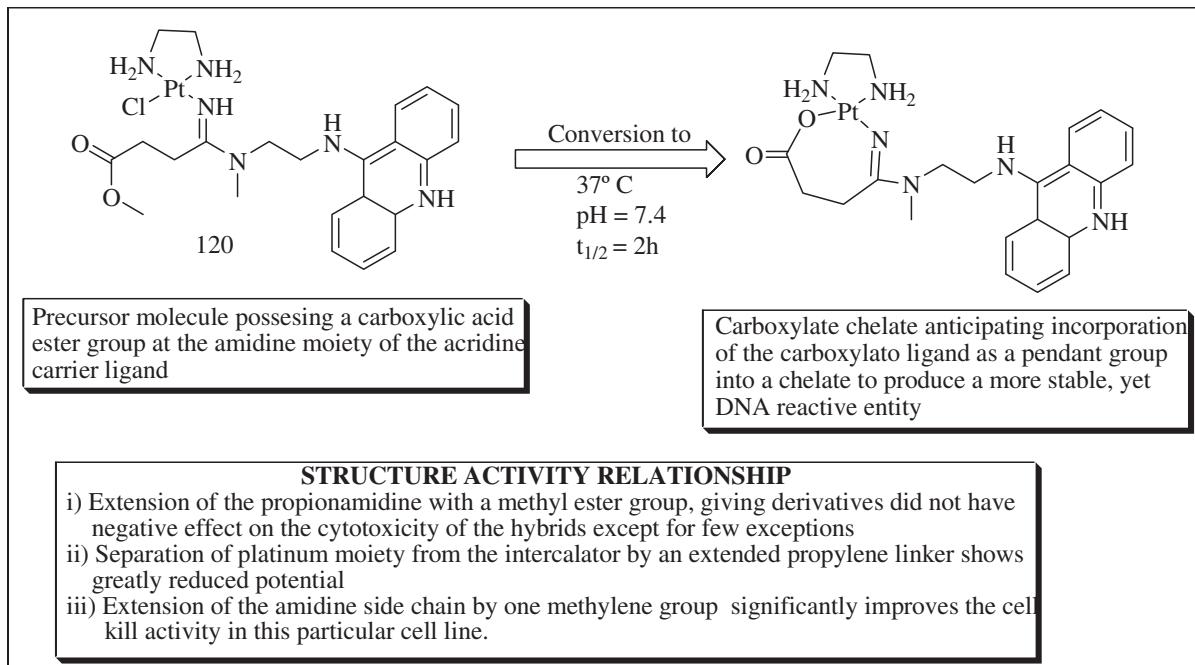
#### 2.6.11. Imidazole scaffold-based 2-benzylbenzofuran [452]

Ability to induce apoptosis and cause cell cycle arrest at G1 Phase of lepidiline A and B is basically attributed to the presence of imidazolium cation [453,454]. The phytoconstituents have displayed promising cytotoxic profile against a panel of human cancer cell lines. Recently, 2-benzylbenzofuran derivatives such as (2, 4-dimethoxyphenyl)-[6-(3-fluorophenyl)-4-hydroxy-3-methylbenzofuran-2-yl] methanone (DMFBM) [454] exhibited potent cytotoxic activities against human lung carcinoma cells. Keeping in view, the anticancer potential of 2-benzylbenzofurans and imidazoles, hybrids of 2-benzylbenzofuran and imidazole (Fig. 77) were synthesised and evaluated *in vitro* against a panel of human tumor cell lines. Hybrids 130 and 131, bearing a 4-methoxyphenyl or naphthylacyl substituent at position-3 of benzimidazole, were found to be the most potent derivatives with  $IC_{50}$  values of  $1.02\text{--}3.57 \mu M$  against all of human tumor cell lines

employed and exhibited cytotoxic activities selectively against breast carcinoma (MCF-7) and myeloid liver carcinoma (SMMC-7721).

#### 2.6.12. 1-deoxynojirimycin – aryl-1, 2, 3-triazoles hybrids as angiogenesis inhibitors [455]

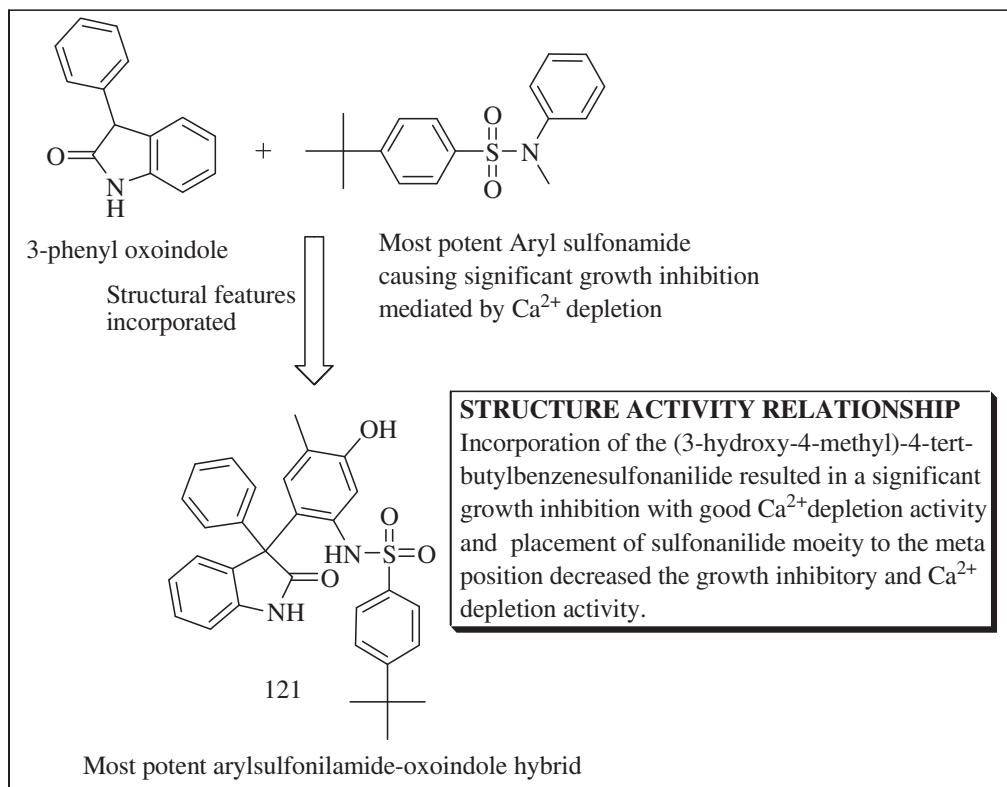
Angiogenesis provides new blood vessels to growing and developing tissues including tumors [456] and is one of the major factors responsible for metastatic spread of malignant tumor cells. Methionine aminopeptidase II [457] and glycosidases represents targets for angiogenesis. Keeping in view, the potential of  $\alpha$ -glucosidases inhibitors, N-methyl-1-deoxynojirimycin, castanospermine and 1-deoxymannojirimycin to alter the biosynthesis of glycans on endothelial cell surfaces that are required for angiogenesis [458] and MetAP2 inhibitory potential of aryl-1,2,3-triazoles [459], Zhou *et al.* designed hybrids of 1-deoxynojirimycin (DNJ) and 5-aryl-1,2,3-triazole (Fig. 78) combining the properties of glycosidase inhibition and MetAP2 inhibition into a single molecule. Hybrids were evaluated for their ability to inhibit  $\alpha$ -glucosidase and inhibition for Bovine aortic

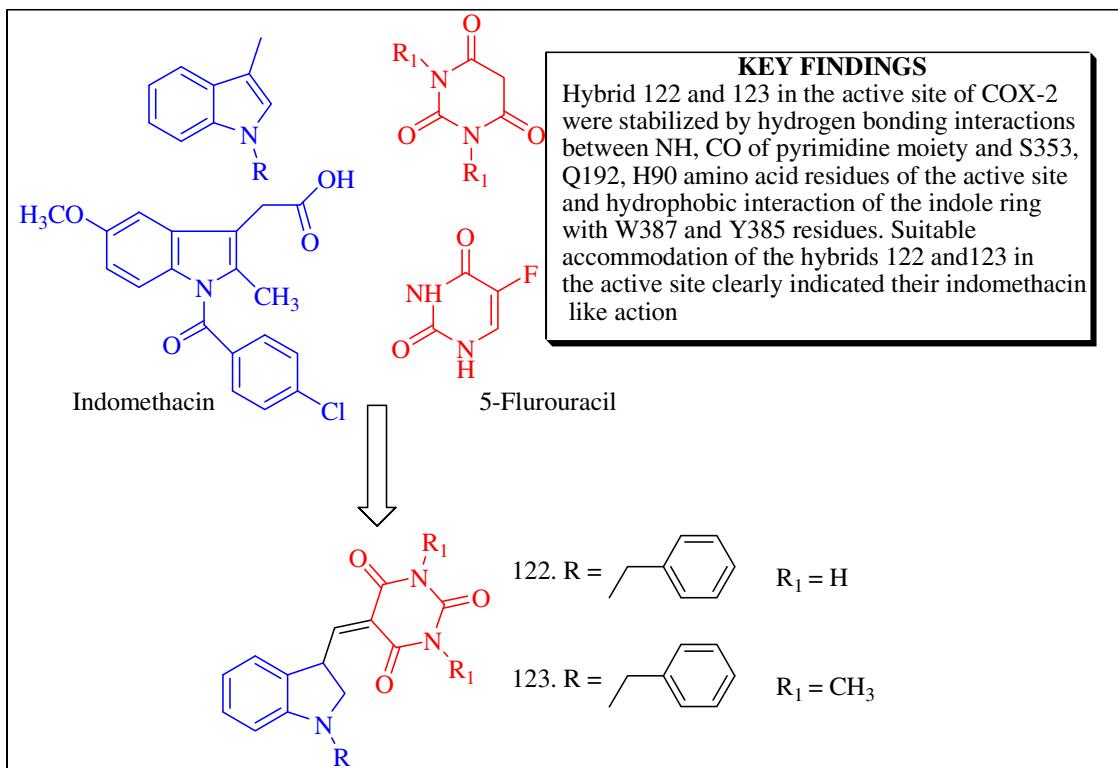
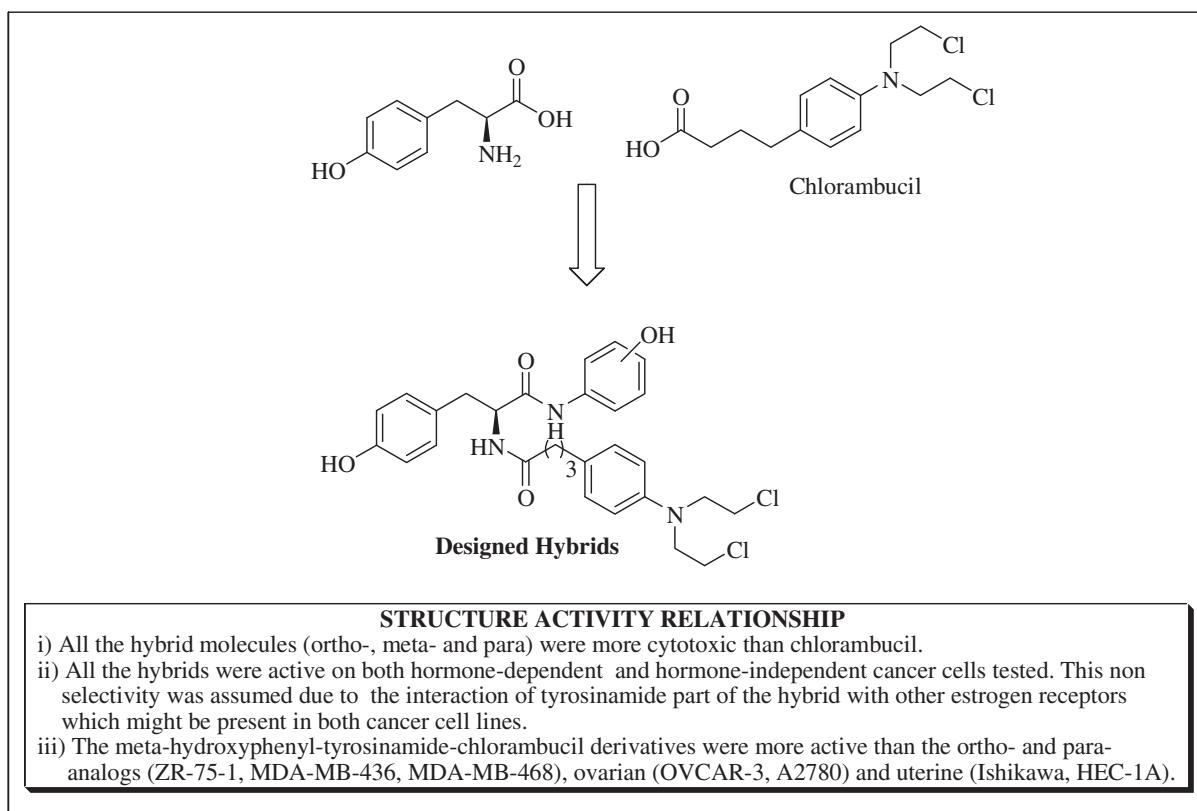
**Fig. 71.** Platinum-acridine hybrids.

endothelial cell growth (BAEC). The hybrid compound 132 ( $\text{IC}_{50} = 1.15 \mu\text{M}$ ) was the most potent inhibitor of  $\alpha$ -glucosidase as well as BAEC growth ( $\text{IC}_{50} = 0.105 \text{ mM}$ ). Hybrid 132 inhibited capillary tube formation similar to capillary-like blood vessels that are formed *in vivo* during angiogenesis.

#### 2.6.13. Novel furozan-based nitric oxide-releasing derivatives of oridonin [460]

Oridonin, natural entkaurene diterpenoid possesses significant anticancer potential exerted through inhibition of nuclear factor  $\kappa\text{B}$  (NF- $\kappa\text{B}$ ) activation, induction of G2/M phase arrest and apoptosis.

**Fig. 72.** Novel arylsulfonylamine-oxindole hybrid.

**Fig. 73.** Indole-barbituric acid hybrids.**Fig. 74.** Tyrosine-nitrogen hybrid molecules.

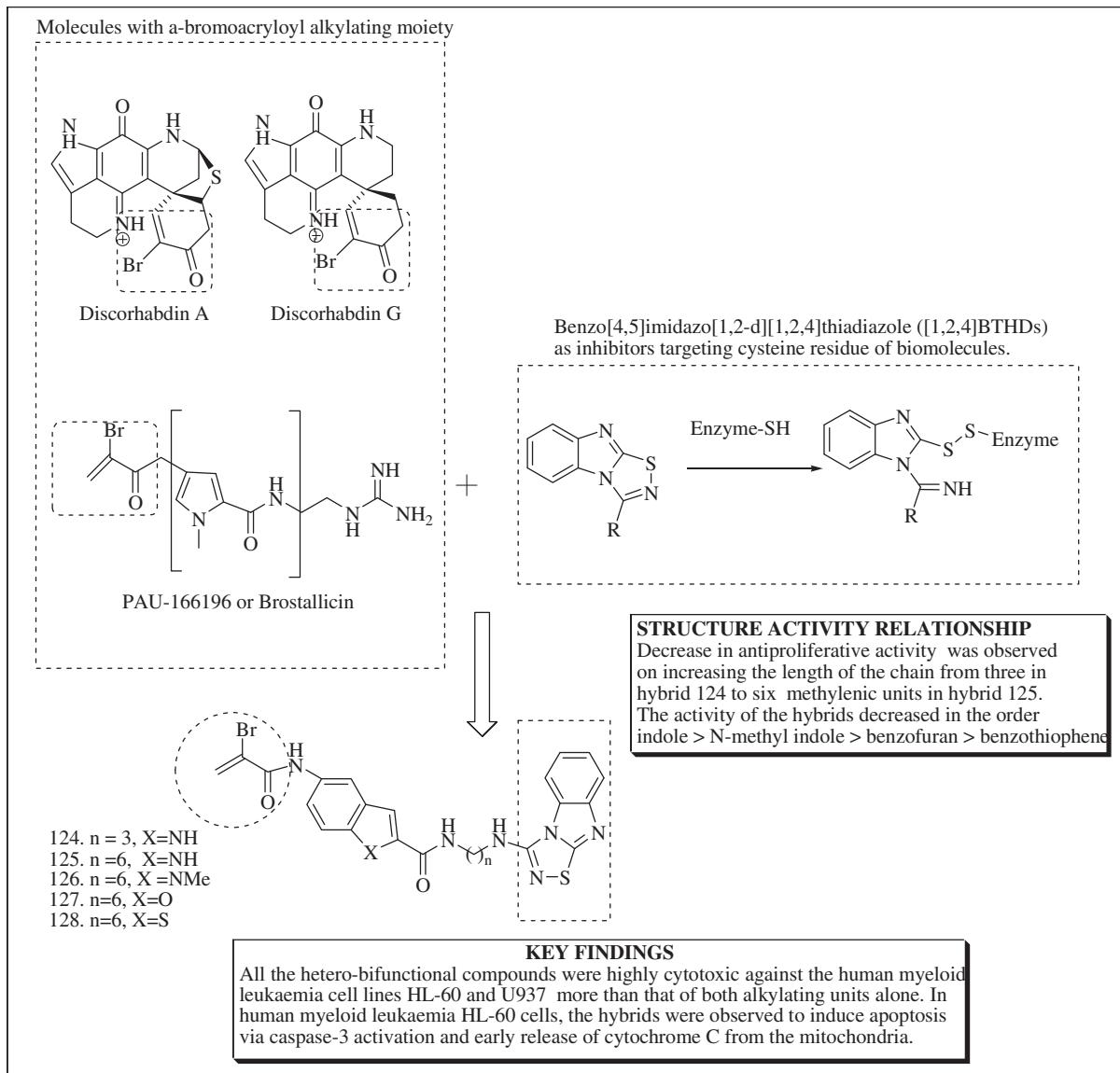


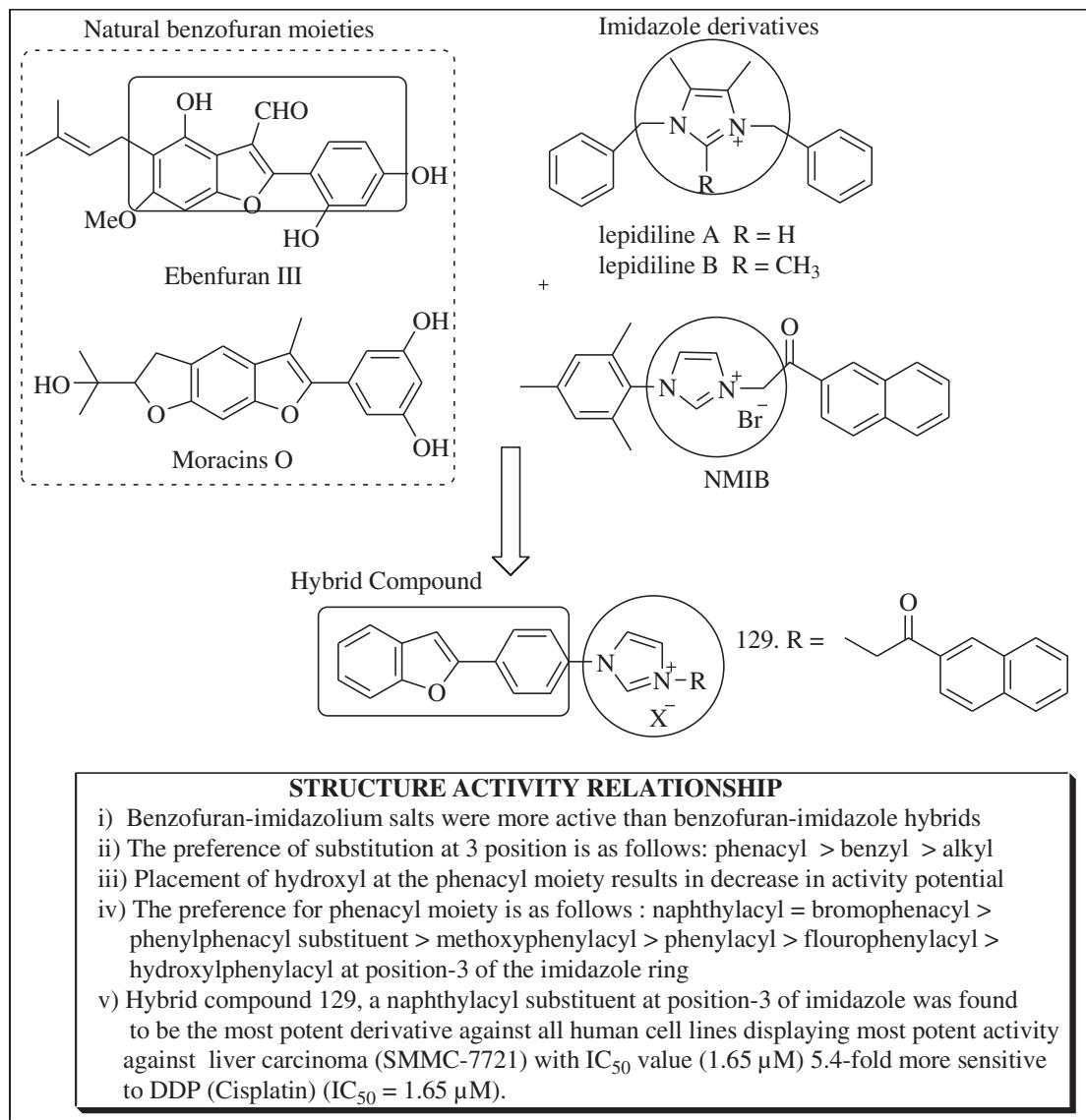
Fig. 75. Benzo [4,5] imidazo [1,2-d] [1,2,4] thiadiazole- $\alpha$ -bromoacryloyl hybrid.

Numbers of oridonin derivatives have been reported with promising anticancer profiles such as 1-O- and 14-O-derivatives of oridonin displaying significant *in vivo* cytotoxicity and also *in-vivo* in mice with H22 liver tumor. These reports along with the nitric oxide donating ability of furoxan which can modify functional proteins, leading to cell cycle arrest and apoptosis, particularly in tumor cells led to the design and synthesis of furozan-oridonin hybrids (Fig. 79). The hybrids were evaluated for nitrate/nitrite levels in the cell lysates, anti-proliferative activity of these hybrids against human cancer cell lines. It was observed that the hybrids produced high levels of NO *in vitro*. Among the synthesised hybrids, hybrid 133 was found to be the most potent exhibiting significant anti-tumor activity with IC<sub>50</sub> values of 1.82  $\mu$ M against K562, 1.81  $\mu$ M against MGC-803 and 0.86  $\mu$ M against Bel-7402, respectively.

#### 2.6.14. Isoflavene-propranolol hybrids [461]

Decreased incidences of certain cancers such as breast and lung cancer associated with the dietary consumption of isoflavones [462,463], in particular, genistein, a predominant isoflavone found in soy products (class of phytoestrogens) led to the investigation on

this class of compounds which yielded a synthetic isoflavene (currently in clinical trials) possessing antiproliferative activity [464] and potential for treatment of drug-resistant ovarian cancer and prostate cancer [465]. With this background and in view of the recently reported enhanced anti-angiogenic and anti-proliferative properties of the 5-fluorouracil and paclitaxel with propanolol, a non-selective beta-blocker [466], Yee *et al.* designed isoflavene-propanolol hybrids (Fig. 80) and evaluated them by anticancer cell viability assays against SHEP neuroblastoma, MDA-MB-231, HMEC-1 human microvascular endothelial cells and MRC-5 human lung fibroblasts and also for anti-angiogenic properties. The results of the biological evaluation revealed that the hybridization of isoflavene with propanolol results in molecules with improved anti-angiogenic and anti-proliferative properties compared to either parent compound alone. The most active hybrid molecules exhibited 30-fold and 4-fold improved potencies against MDA-MB-231 breast adenocarcinoma and SHEP neuroblastoma cancer cell lines, respectively. Among the hybrids, hybrid 134 and 135 were the most active against SHEP and MDA-MB-231 cells compared to isoflavene. Hybrid 134 possessed GI<sub>50</sub> values of 0.7, 2.9  $\mu$ M (MDA-



**Fig. 76.** 2-phenylbenzofuran-imidazole hybrids.

MB-231), 3.0 μM (SHEP) While Hybrid 135 possessed GI<sub>50</sub> values of 2.0 μM (MDA-MB-231), 2.8 μM (SHEP). These hybrids retained significant selectivity for cancer cells over MRC-5 normal lung fibroblast cells.

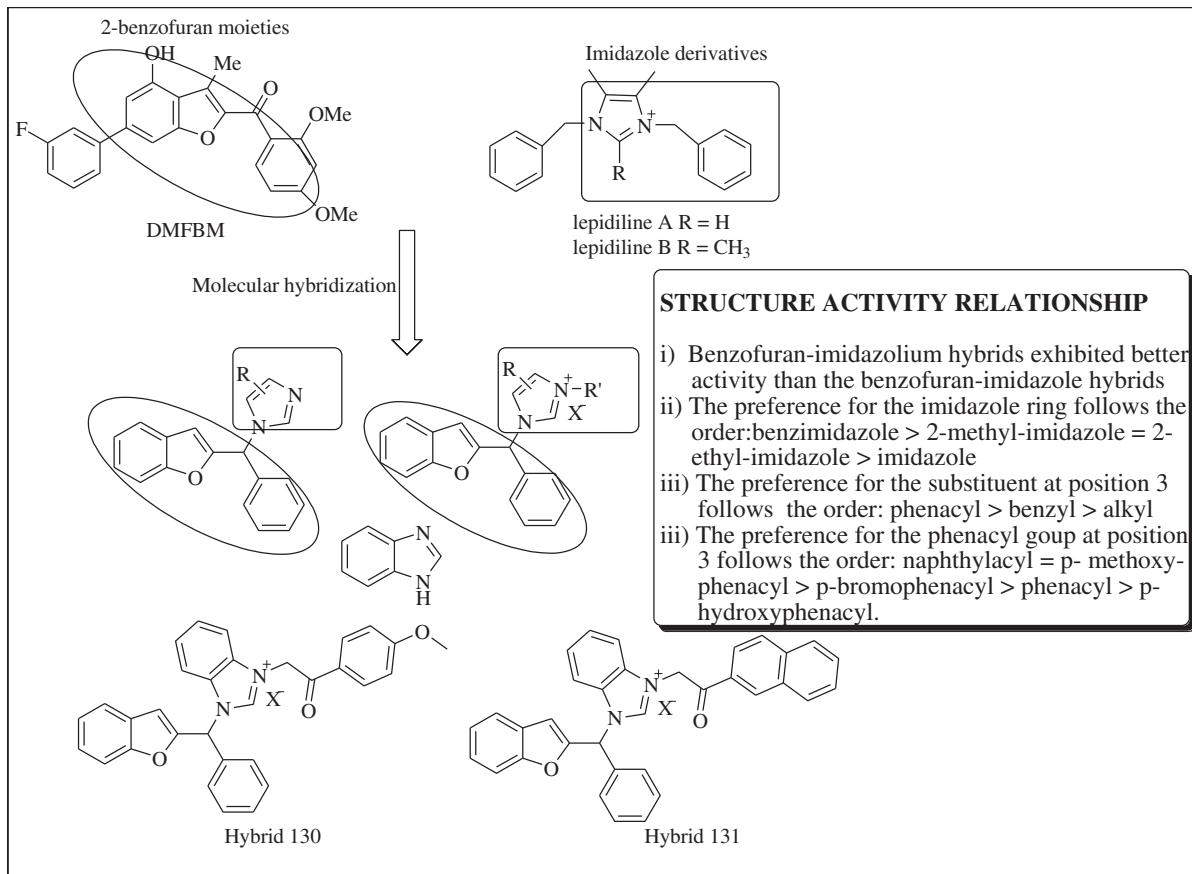
#### 2.6.15. Dithiocarbamates-triazole hybrids [467]

Dithiocarbamate derivatives are known to possess diverse array of biological activities such as anti-fungal [468], anti-bacterial [469] and carbonic anhydrases inhibitor [470,471]. Recent reports on the anticancer potential of butenolide-containing dithiocarbamates [472,473] motivated the research group lead by Duan *et al.* to fuse them with triazole. Significant anticancer potential of Brassinin, a phytoalexin in cruciferous plants (possessing a dithiocarbamate moiety), sulforamate molecule resulting from structural modification of brassinin and novel butenolide containing dithiocarbamates reported led to their inclusion. Due to their properties such *in vivo* stability, aromatic stabilization, hydrogen bonding ability and appropriate dipole moment [474,475], triazoles have gained enough attention in the recent past. With this background, a series of novel 1,2,3-triazole-dithiocarbamate hybrids were designed

(Fig. 81), synthesized and evaluated for anticancer activity against four selected human tumor cell lines (MGC-803, MCF-7, PC-3, EC-109). Hybrids 136 and 137 displayed broad spectrum of anti-cancer activity *in vitro*. Hybrid 136 (IC<sub>50</sub> = 0.73–11.61 μM) was more potent than 5-fluorouracil against all tested human cancer cell lines.

#### 2.6.16. 1,2,3-triazole-dithiocarbamate-urea hybrids [476]

In continuation of their attempts to design potent dithiocarbamate bases hybrids encouraged by the promising results of the previously reported 1,2,3-triazole-dithiocarbamate by the same research group in the same year motivated Duan *et al.* to design 1,2,3-triazole-dithiocarbamate-urea hybrids in view of anticancer activity of urea derivatives including ureas, arylureas, and thioureas. The designed hybrids (Fig. 82) were synthesised and evaluated for antiproliferative activity against four human cancer cell lines, MGC-803 (human gastric cancer cell line), MCF-7 (human breast cancer cell line), SMMC-7721 (human hepatocellular carcinoma cell line) and EC-9706 (human esophageal cancer cell line). Hybrid 138 exhibited broad

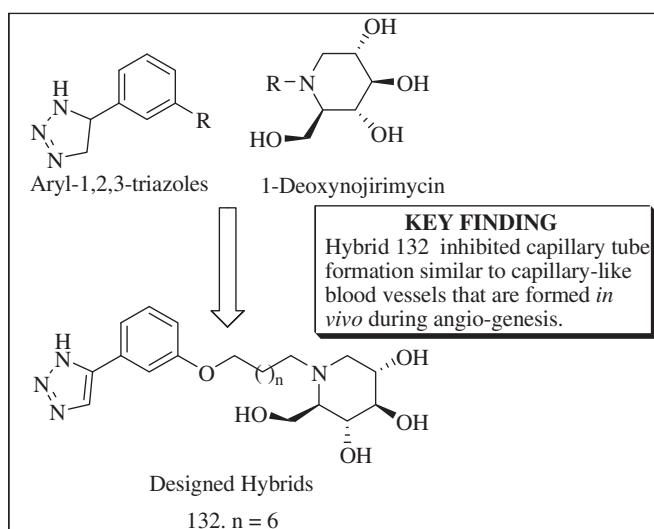


**Fig. 77.** Imidazole scaffold-based-2-benzylbenzofuran.

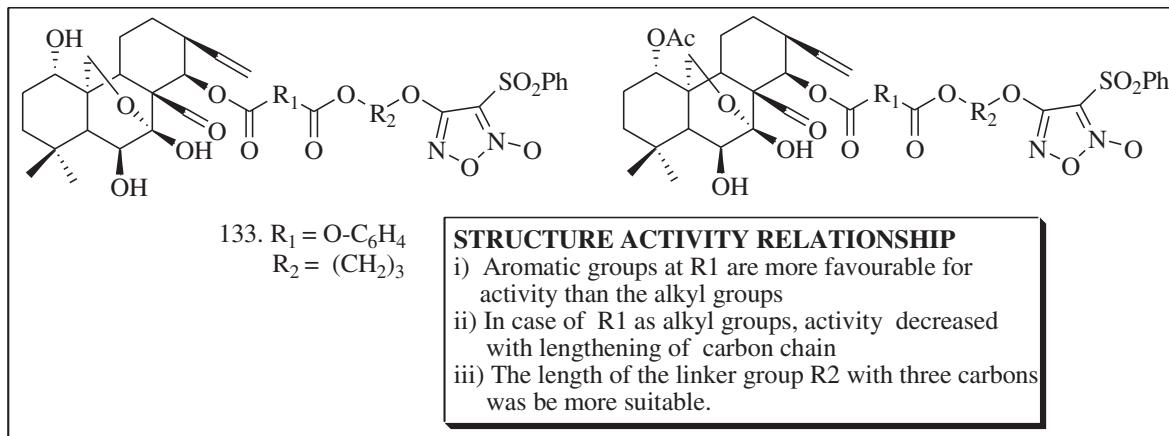
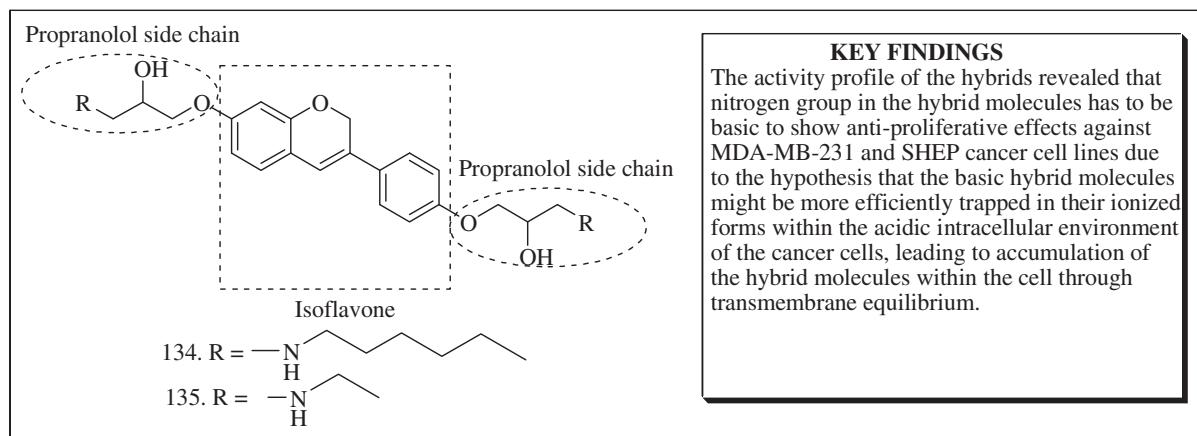
spectrum anticancer activity with IC<sub>50</sub> values ranging from 1.62 to 20.84 μM and 0.76–13.55 μM respectively. The hybrids were most active against MGC-803 cells and did not possess significant cytotoxicity against normal human embryonic kidney cells at up to 55 μM and 70 μM, respectively. The hybrid was found to cause cell cycle arrest at G2/M phase and induce apoptosis.

#### 2.6.17. Tetrahydro-β-carboline-1,3,5-triazine hybrids [477]

The presence of β-carboline nucleus (tricyclic pyrido [3,4-b] indole ring) in harman and norharman derivatives [478], manzamine [479], eudistomine K [480], azatoxin [481], fascaplysin [482] and picrasidine L [483] is well reported. These molecules are known to display potent cytotoxic activities against various cancer cell lines through varied mechanisms. Similarly, the cytotoxic

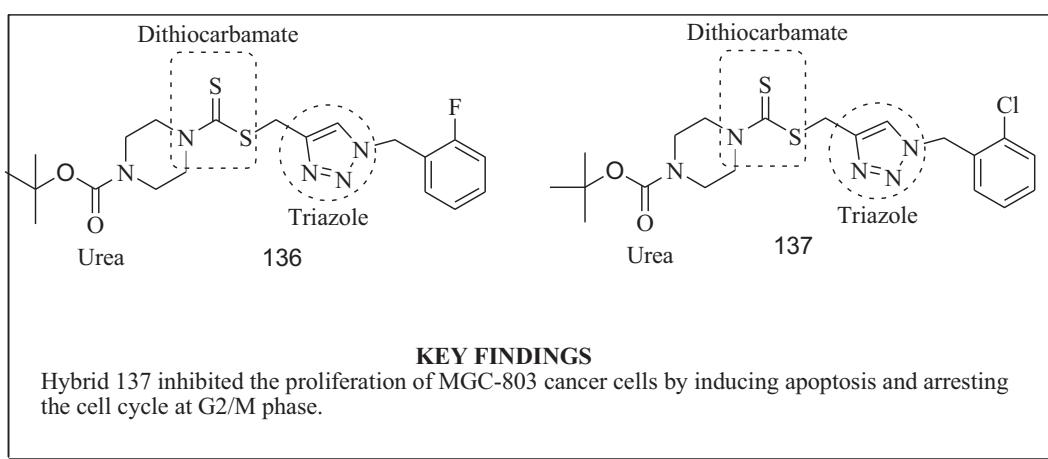


**Fig. 78.** 1-deoxynojirimycin-aryl-1, 2, 3- triazoles hybrids.

**Fig. 79.** Novel Furozan-based nitric oxide-releasing derivatives of oridonin.**Fig. 80.** Isoflavene-propranolol hybrids.

profile of molecules possessing the 1,3,5-triazine skeleton such as hexamethylmelamine (effective agent against breast, lung and ovarian cancer) [484], irsogladine (possessing anti-tumor activity in murine xenograft models of epidermoid cancer and glioma [485] and also active against breast cancer cells), some recently reported molecules with triazine skeleton possesing microtubule

destabilizing activity [486], p38 MAP kinase inhibitory activity [487], (cyclin dependent kinases inhibitory activity) [488] and tyrosine kinase inhibitory activity [489] highlights the anticancer potential of the triazine skeleton. With this background, hybrids of these functionalities were designed (**Fig. 83**) and evaluated for *in vitro* cytotoxic activity on human cancer cell lines representing

**Fig. 81.** Dithiocarbamates-triazole hybrids.

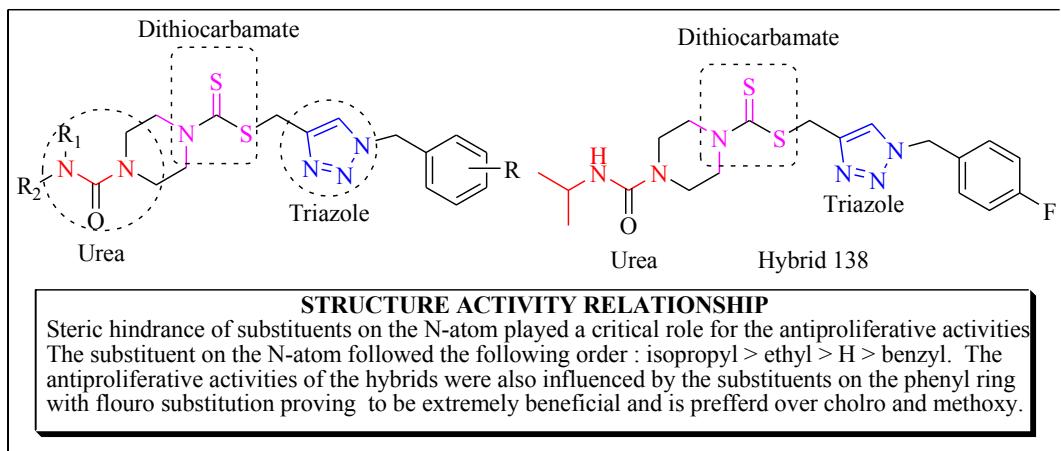


Fig. 82. 1, 2, 3-triazole-dithiocarbamate-urea hybrids.

breast cancer (MCF7), colon (SW620), prostate (DU145), oral (KB), ovary (PA1), leukemia (K562), pancreas (MiaPaCa-2), lung (A549) and normal fibroblasts (NIH3T3) by Kumar *et al.* The results of the *in-vitro* assay revealed that hybrids 140, 141 and 142 were selectively toxic towards KB (oral cancer) cell line with IC<sub>50</sub> values of 105.8, 664.7 and 122.2 nM.

#### 2.6.18. Fragment based approach for hybrid G – quadruplex ligands [490]

G-quadruplexes, special secondary structures adopted in some guanine-rich DNA sequences are present in important regions of the eukaryotic genome [491,492]. Such structures may play important roles in the regulation of biological events in the body and have thus become valid targets for new anticancer drugs in the recent pasts. The structural features of previously reported G-quadrupole binding ligands are well defined such as presence of large number of aromatic/heteroaromatic unit locked into a planar disposition [492,493] for providing extra stabilization through π stack onto the terminal tetraplex of the quadruplex [493,494], side chains possessing positive charge or potential to become protonated at physiological pH, sites for

electrostatic interactions with the negatively charged phosphate where they proposed residues in the grooves [494]. With this background, Ritson *et al.* in 2012 in continuation of their previous studies on triazole based quadruplex binding 'click' ligands [495] inspired by tolmestatin where they proposed that 1,4-triazole moiety would serve as a suitable mimic of the oxazole functionality of telomestatin (Class 1) and later confirmed that rotational freedom of polyaromatic rings is a prerequisite for selectivity for quadruplex DNA (Class 2), designed and synthesised hybrid G-quadruplex ligands with combined features of tolmestatins utilizing copper catalyzed click chemistry approach. Fig. 84 represents the employed rational design approach. The structural features of the designed molecules involved the following points: i) non-fused polyaromatic system ii) minimum conformational flexibility iii) number of heteroaromatic units in the ligands for stacking interactions and maximizing interactions between electron rich ligand heterocycles and guanine residues iv) oxazole skeleton of tolmestatin along with 1, 4 triazole and side chain functionalities (Class 1) as per previous studies by the same research group. The ability of these compounds to stabilize G-quadruplex and double helix DNA was investigated using a

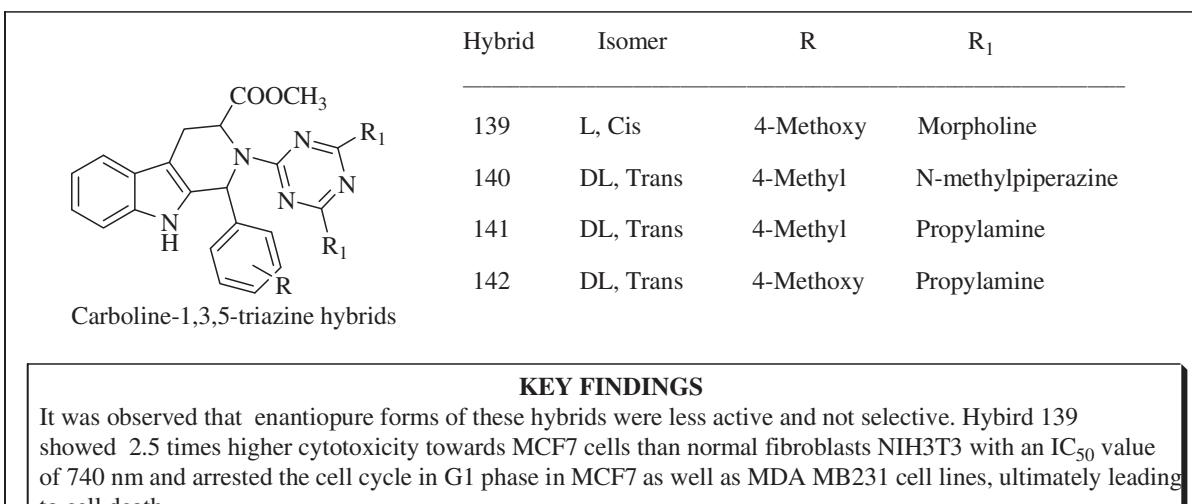
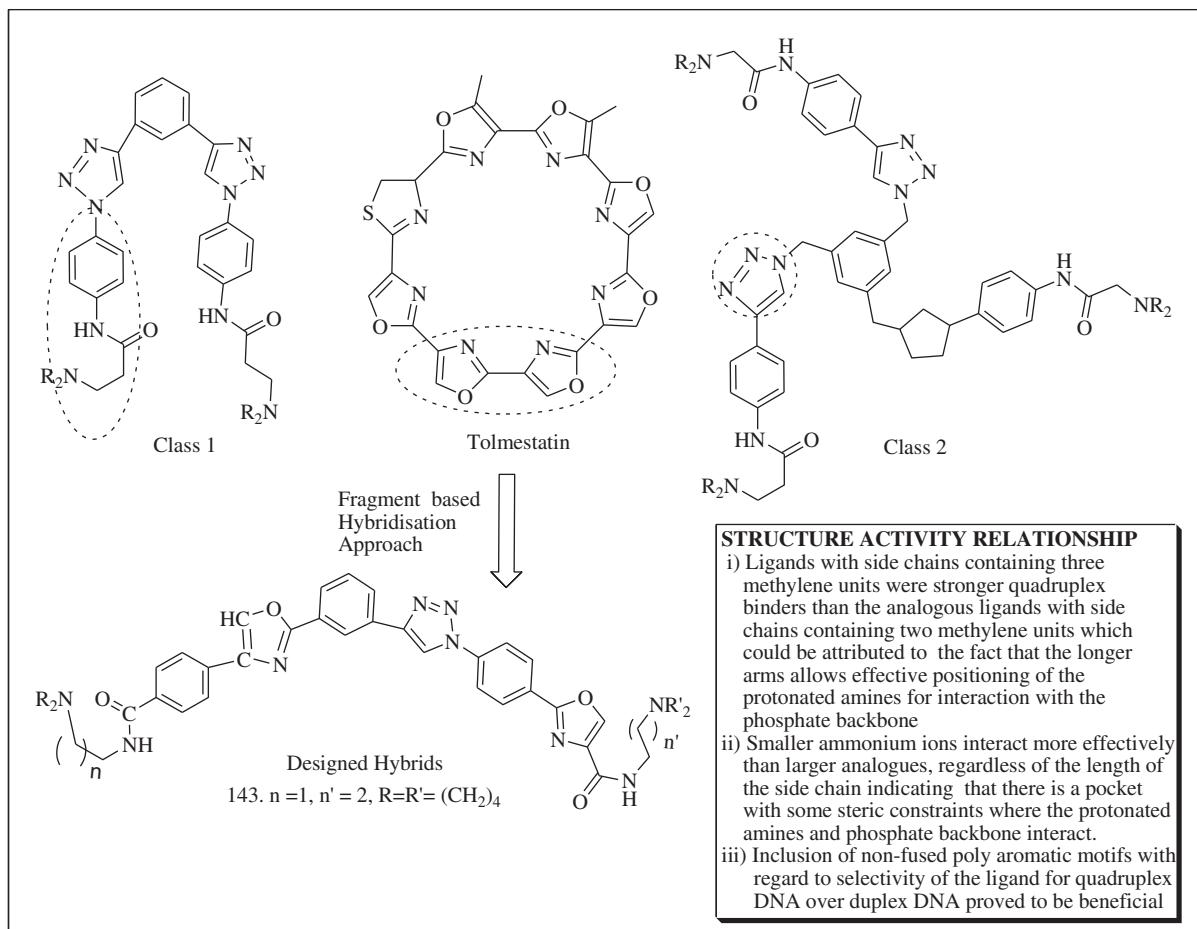


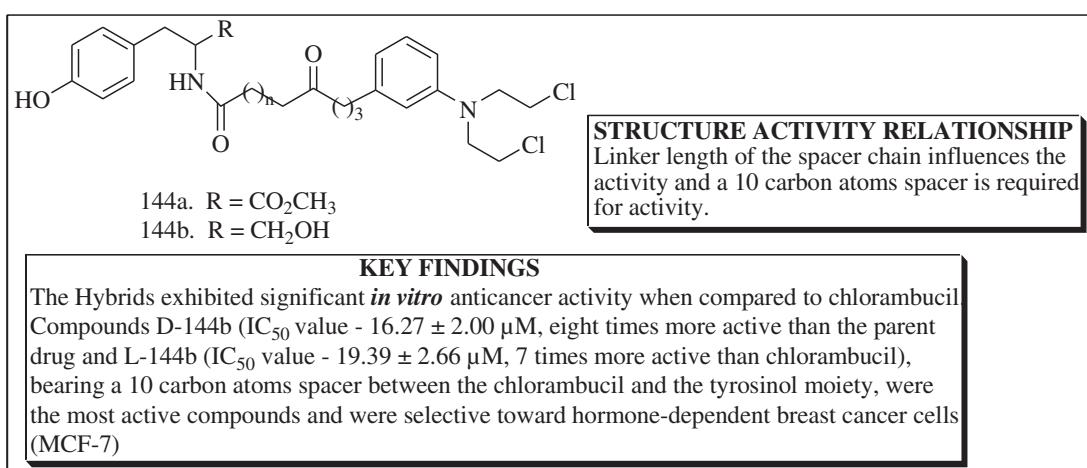
Fig. 83. Tetrahydro-β-carolene-1, 3, 5-triazine hybrids.

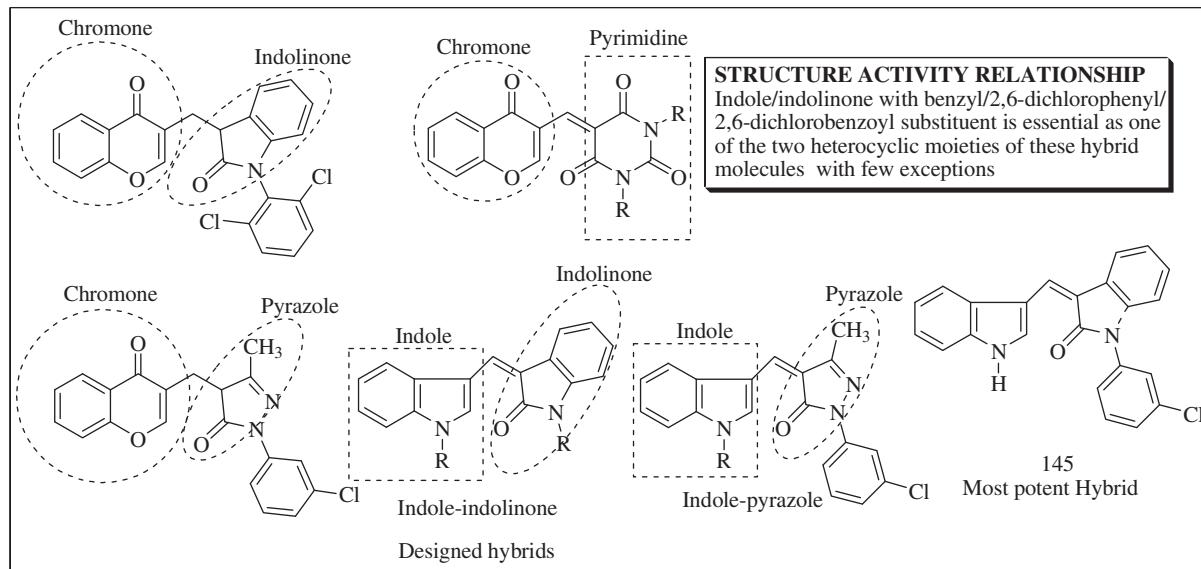
**Fig. 84.** Fragment based approach for hybrid G-quadruplex ligands.

high-throughput FRET (fluorescence resonance energy transfer) assay. Among the hybrids, Hybrid 143 is most interesting, which displayed complete selectivity for quadruplex DNA over duplex DNA, even at a concentration of 4  $\mu\text{M}$  and showed a small amount of stabilization of human telomeric sequence a concentration of 1  $\mu\text{M}$ .

### 2.6.19. D- and L- tyrosine-chlorambucil analogs [438]

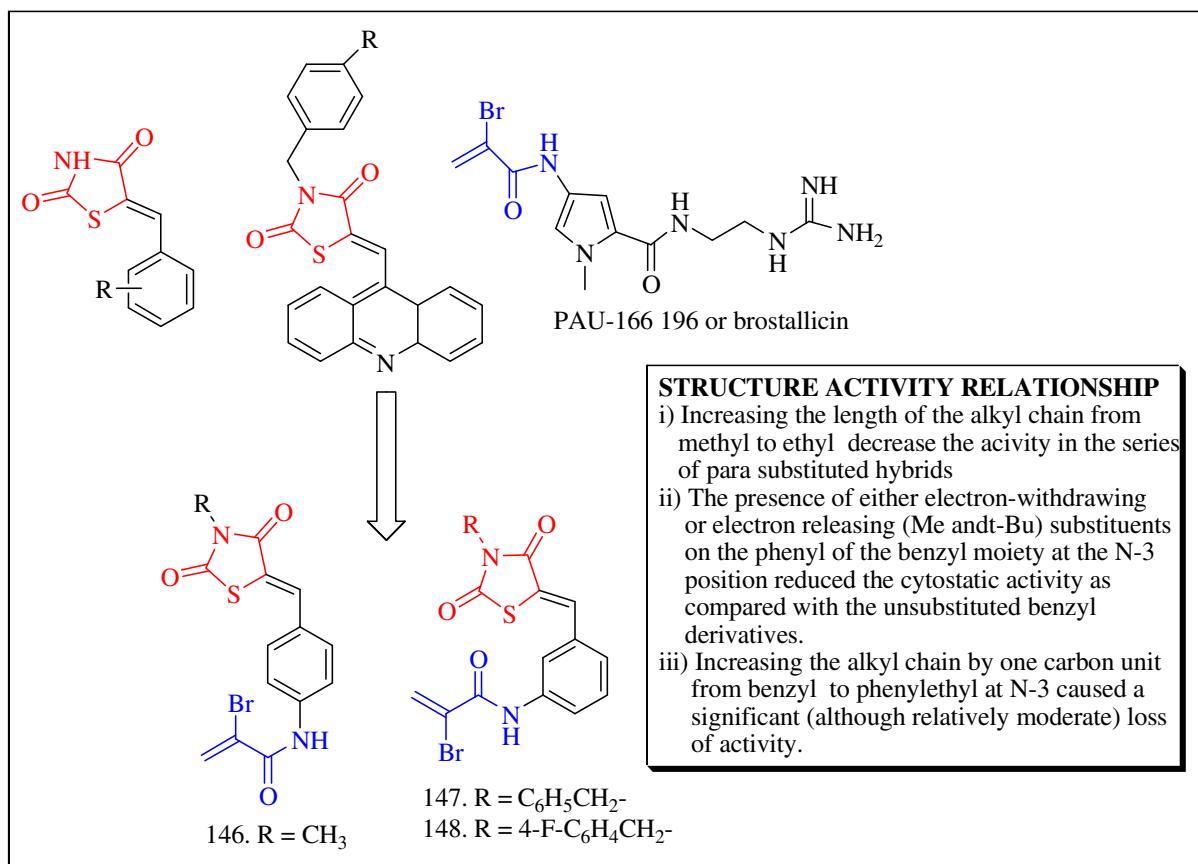
Estradiol, the female sex hormone, binds to its receptor and then activates transcription factors and triggers proliferation [496]. In this context, estardiol -linked-drugs have shown promising *in vitro* biological activity with selectivity for hormone-dependent breast cancer [497]. Attention has also been made towards non-steroidal

**Fig. 85.** D- and L-tyrosine-chlorambucil analogs.

**Fig. 86.** Indole, pyrazole, chromone and pyrimidine based conjugates.

cytotoxic hybrid molecules with the aim of destroying cancerous cells without activating the ER- $\alpha$ . In the past, hybrids comprising a chemotherapeutic agent and an amino acid have also shown promising *in vivo* results [498] and chlorambucil conjugates with lipidic amino acids were also developed as anticancer agent. Keeping this in view, a series of D- and L- tyrosine-chlorambucil

analogs was synthesized as anticancer drugs for chemotherapy of breast cancer. Chlorambucil (CHL) is a bis-alkylating agent which belongs to the nitrogen mustard family and is used to treat chronic lymphocytic leukemia and malignant lymphomas. It is also useful for the treatment of solid tumors such as advanced ovarian and breast carcinoma [499]. The newly synthesized compounds

**Fig. 87.**  $\alpha$ -bromoacryloylamido-5-benzylidene thiazolidine-2,4-dione.

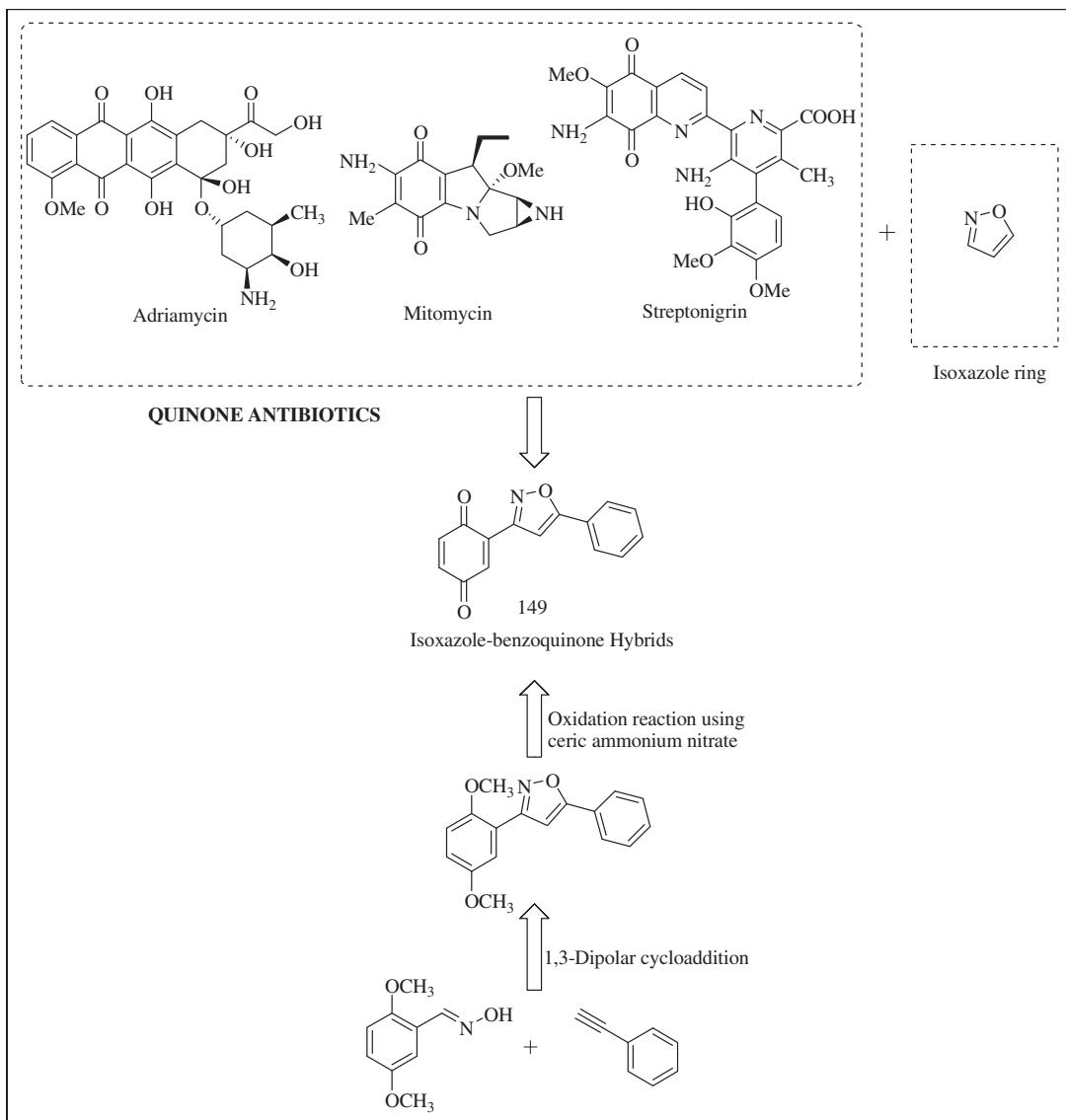


Fig. 88. Isoxazole-benzoquinone hybrids.

(Fig. 85) were evaluated for their anticancer efficacy in different hormone-dependent and hormone-independent (ER+ and ER-) breast cancer cell lines. Chlorambucil was linked to the tyrosine framework at the  $\alpha$ -amine function for appropriate placement of functional groups possibly involved in the receptor recognition.

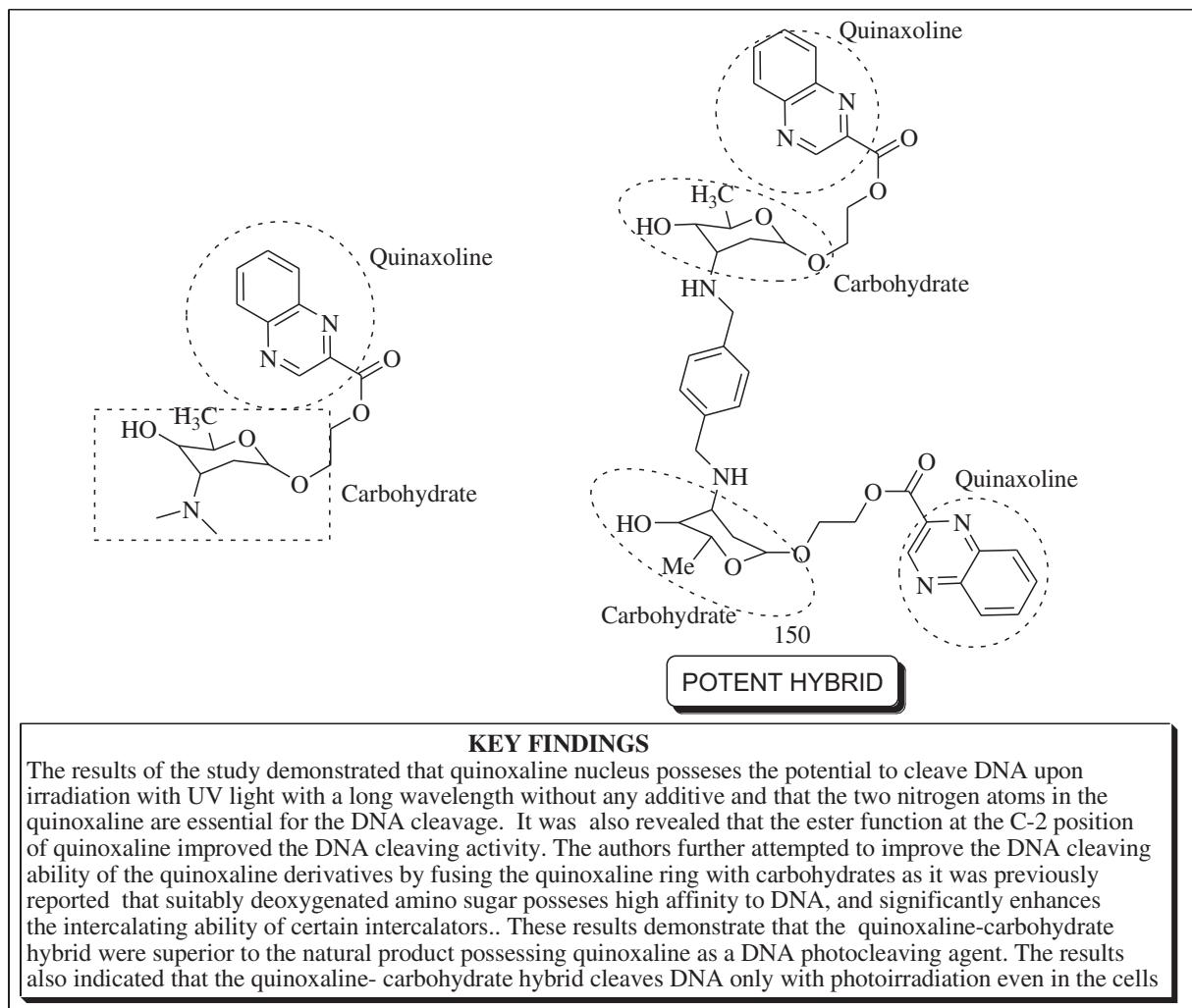
#### 2.6.20. Indole, pyrazole, chromone and pyrimidine based conjugates [500]

Singh *et al.* in 2010 designed and synthesised indole, pyrazole, chromone and pyrimidine based conjugates (Fig. 86) in view of the presence of these privileged heterocycles in currently available anticancer drugs such as 5-fluorouracil [501,502], indomethacin [503,504], taxol [505,506], doxorubicin [507], mitoxantrone [508,509], indirubin [510], celecoxib [511,512], hydrazinecarbothioamide [513] and anticancer potential of flavonoids [514] and tested them for tumor growth inhibitory activities over 60 human tumor cell lines. Conjugates exhibited  $GI_{50}$  (over 60 human tumor cell lines) in the range 1.7  $\mu\text{M}$ –3.2  $\mu\text{M}$  and *in vitro* therapeutic indices ( $LC_{50}/GI_{50}$ ) 30.5, 18.9, 10.0, 17.5, and 13.7, respectively. The docking interactions of conjugates in the active sites of RNR, TS, TP

and COX-2 clearly indicated that they were well accommodated via hydrogen bonding and hydrophobic interactions.

#### 2.6.21. $\alpha$ -Bromoacryloylamido-5-benzylidene thiazolidine-2, 4-dione [515]

Romagnoli *et al.* fused  $\alpha$ -bromoacryloyl unit and the 5-arylidene thiazolidine-2, 4-dione scaffold (possessing  $\alpha$ ,  $\beta$ -unsaturated carbonyl system which can act as Michael acceptors) to synthesize hybrids containing a pair of Michael acceptors in their structures. Molecules with thiazolidine-2, 4-dione scaffold have been reported as antineoplastic agents with a broad spectrum of anticancer activity [516]. Moreover, 5-benzylidene-thiazolidine-2, 4-dione core has also been identified as Pim-1 protein kinase inhibitors [517]. With this background, a series of such hybrids (Fig. 87) were synthesised and evaluated for antiproliferative effects against the growth of murine leukemia (L1210), murine mammary carcinoma (FM3A), human T-lymphoblastoid (CEM) and human cervix carcinoma (HeLa) cells. Hybrid 146, 147, 148 displayed promising results with  $IC_{50}$  range of 0.19–0.87  $\mu\text{M}$ , 0.38–1.4  $\mu\text{M}$  and 0.68–0.92  $\mu\text{M}$ . Detailed biological evaluation indicated that conjugates suppress



**Fig. 89.** Quinoxaline-carbohydrate hybrids.

proliferation of human myeloid leukemia HL-60 and U937 cells by triggering morphological changes and internucleosomal DNA fragmentation, which are well-known features of apoptosis. The apoptosis inducing ability of hybrids 146–148 was accompanied by cleavage of the nuclear protein PARP, a recognized caspase-3 substrate which is involved in DNA repair.

#### 2.6.22. Isoxazole-benzoquinone hybrids [518]

The quinone containing compounds have been widely used for their antitumor and anticancer activities [519]. Quinone antibiotics such as adriamycin, mitomycin C, and streptonigrin [520] are reported to interfere with the synthesis of DNA as well as RNA. Isoxazole represents another class of heterocycles with diverse array of biological attributes [521]. Speculating potent anticancer activity of quinone-isoxazole hybrids, Kumar *et al.* proposed an efficient method for the preparation of novel 2-(5-arylisoaxazol-3-yl)cyclohexa-2,5-diene-1,4-dione hybrids via 1,3-dipolar cycloaddition followed by an oxidation reaction using ceric ammonium nitrate (CAN) (Fig. 88).

#### 2.6.23. Quinoxaline–carbohydrate hybrids [522]

Quinoxaline skeleton is present in antitumor antibiotics [523] such as echinomycin and triostin A which are well reported DNA intercalators [524]. Toshima *et al.* in 2003 examined the photo-

induced DNA cleaving activities of the quinoxaline derivatives using supercoiled  $\phi$ X174 DNA in view of the presence of conjugated C=N group expected to generate photo excited n– $\pi^*$  and  $\pi$ – $\pi^*$  states by photo irradiation which could be capable of cleaving DNA by H-abstraction, electron-transfer, and/or singlet oxygen oxidation pathway. The cytotoxicity of the hybrids was tested against HeLa S3 and MDA-MB-231 with or without photo irradiation. The quinoxaline–carbohydrate hybrids (Fig. 89) exhibited strong and selective cytotoxicity against cancer cells with photo irradiation. Hybrid 150 with photo irradiation was most active against HeLa S3 with an IC<sub>50</sub> value of 1  $\mu$ M.

#### 2.6.24. Hybrid acetogenins [525]

Inhibition of multidrug resistant cancer cells with the ATP-driven transport system by acetogenins has been one of the prime reasons for the attention of the researchers. Acetogenins are polyketides possessing tetrahydrofuran rings linked with  $\alpha$ ,  $\beta$ -unsaturated- $\gamma$ -lactone ring via a long hydrocarbon chains [526]. With this background, kojima *et al.* in 2008 designed a series of hybrids encompassing: i) Structural motifs of pesticides targeting mitochondrial complex i.e. nitrogen containing heterocycles and a hydrophobic chain ii) tetrahydrofuran ring of acetogenins (solamin, a mono-THF acetogenin was selected as a lead compound). The authors employed retro synthetic route for the synthesis of desired

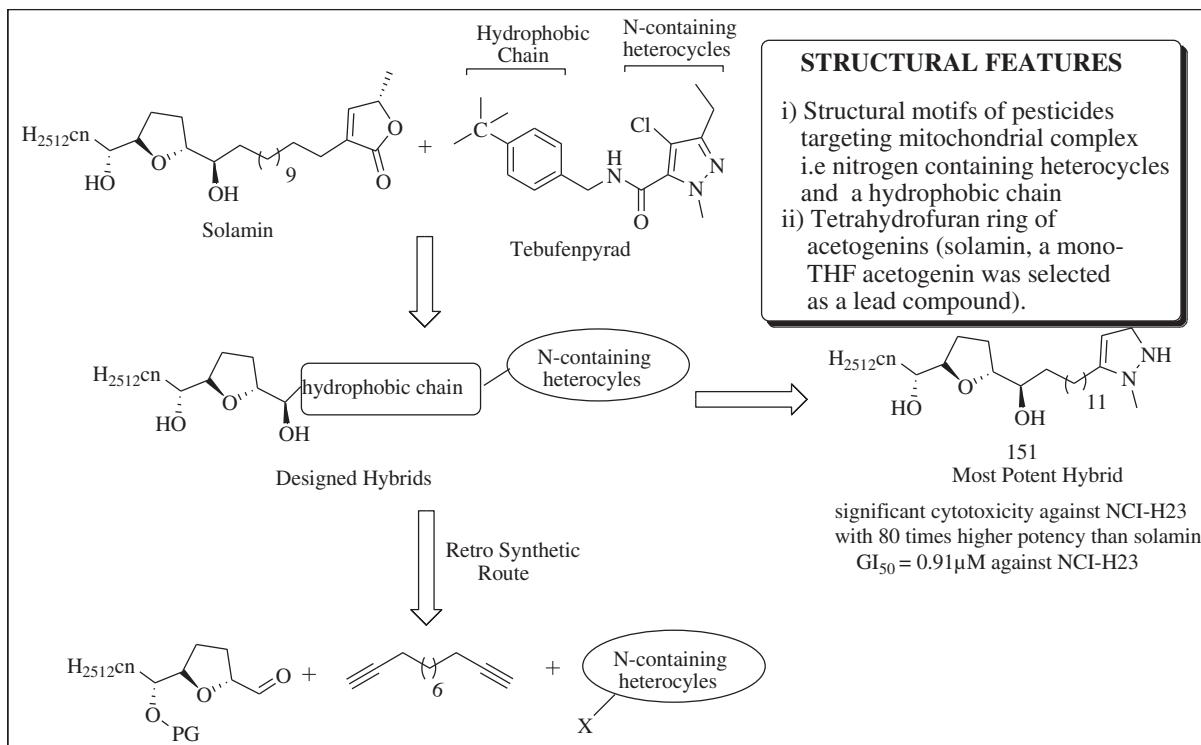


Fig. 90. Hybrid acetogenins.

compounds (Fig. 90). Thus a series of  $\alpha$ ,  $\beta$ -unsaturated- $\gamma$ -lactone-free nitrogen-containing heterocyclic analogues of solamin, a natural mono-THF acetogenin, was synthesized and their cytotoxicity was investigated against 39 tumor cell lines. One of them, 1-methylpyrazol-5-yl derivative (Hybrid 151), showed selective increase of cytotoxicity against NCI-H23 with 80 times higher potency than solamin.

Kojima et al. [527] in continuation of their study designed a new series of annonaceous acetogenins employing amide based linker (Fig. 91) for connecting the heterocyclic part with the hydrophobic part in view of the fact that the heterocycles of most insecticides are linked to the hydrophobic parts with an amide group. Amide-connected analogue 152 showed selective and very potent activity ( $<10$  nM) against some cancer cell lines.

#### 2.6.25. Platinum-acridine hybrid agents modified with bipyridine non-leaving groups [528]

Kheradi et al. in 2009 investigated the use of 2,2-bipyridines as non-leaving groups (L-L) in platinum-acridinylthiourea

conjugates (Fig. 92) in a search for novel mechanisms of modulating the reactivity of the metal center to accelerate substitution reactions in Pt (II) complexes through  $\pi$ -backbonding effects. A common structural feature in the bipyridines – substituted complexes appears to be the intramolecular  $\pi$ -stacking at van der Waals contact distance of the acridinium chromophore with the Pt (bpy) moieties. The hybrids (154–157) displayed micromolar activity in HL-60 (leukemia) and H460 (lung) cancer cell lines but were significantly less potent than the prototypical compound (153) containing aliphatic ethane-1, 2-diamine. The reduced activity was attributed to the relative lability of the DNA adducts they form. The results indicated that bipyridines accelerated the reaction of platinum with DNA nitrogen, but the resulting adducts are more labile than those formed by the prototype.

#### 2.6.26. NSAID based hybrids

ASPIRIN-NO Hybrid was designed by linking aspirin with a nitrate group as an NO donor through a spacer. Aspirin is a known moderately active chemo preventive agent and it was assumed that

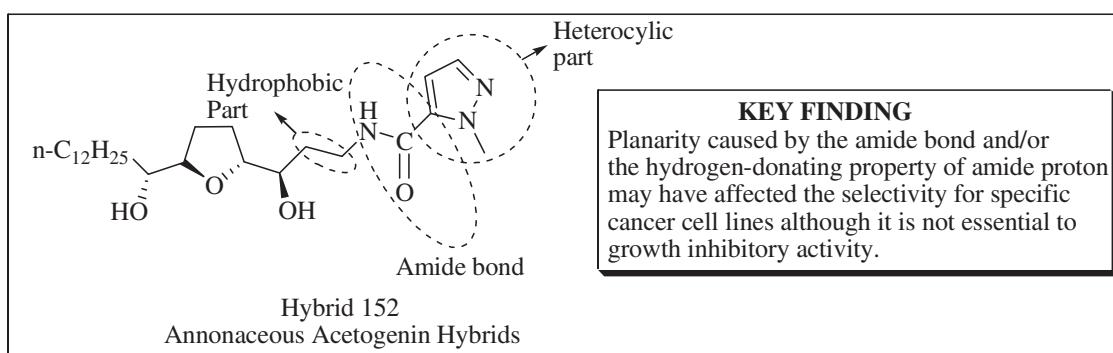
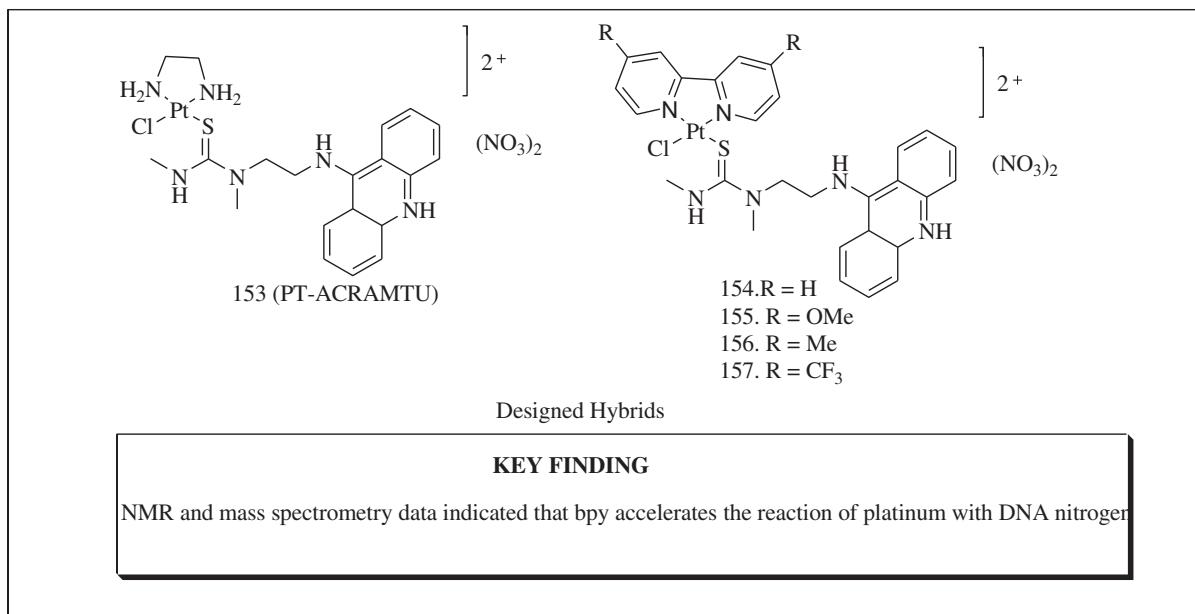


Fig. 91. Hybrid acetogenins.



**Fig. 92.** Platinum-acridine hybrid agents modified with bipyridine non-leaving groups.

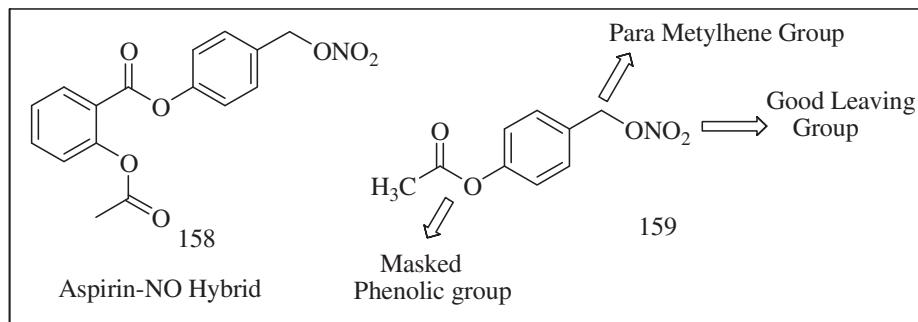
the designed hybrids would allow the concomitant release of NO to reduce the gastrointestinal side effects of Aspirin [529,530]. With this background, Hybrid 158 (Fig. 93) was synthesised and was found to be highly effective in inhibiting growth of colon cancer both *in vitro* and *in vivo* [531,532]. This motivated the research group led by Wijtmans in 2007 to carry an in depth investigation on the mechanistic insights of the NO-NSAID hybrids and synthesised benzyl nitrate 159 (Fig. 93) for this purpose. However the study provided some conflicting reports about the mechanism of the antitumor effects and revealed that neither Aspirin nor NO contributes to this antitumor effect. It is rather, an unsubstituted Quinone methide (Fig. 94) which was identified as the agent responsible for the cell killing potential. It was recognized that the core skeletons of 158 and 159 (benzyl nitrate by the author) in fact satisfy the requirements for precursors to the class of para-Quinone Methides. The design of such precursors requires the presence of an aromatic ring substituted with a masked phenolic group and a paramethylene group attached to a good leaving group. QMs are highly electrophilic species and reacts with cellular nucleophiles such as GSH or DNA to act as cytotoxic agents [533].

Another NSAID based Hybrid with an H<sub>2</sub>S and NO donor moieties (Fig. 95) have also been reported (Hybrid 160). One arm of the hybrid aspirin releases nitric oxide (NO), which helps protect the stomach lining. The other releases hydrogen sulfide (H<sub>2</sub>S), which

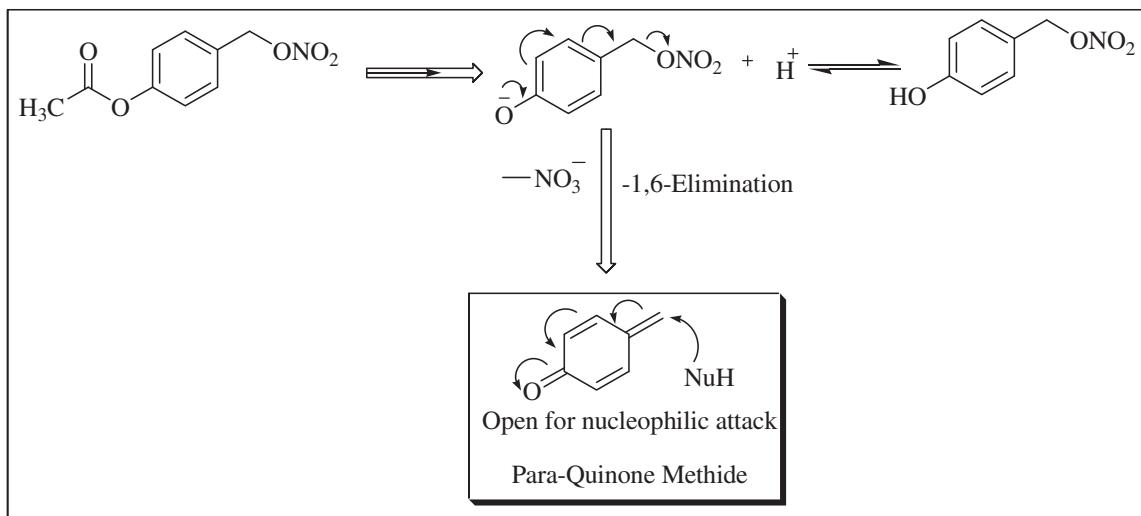
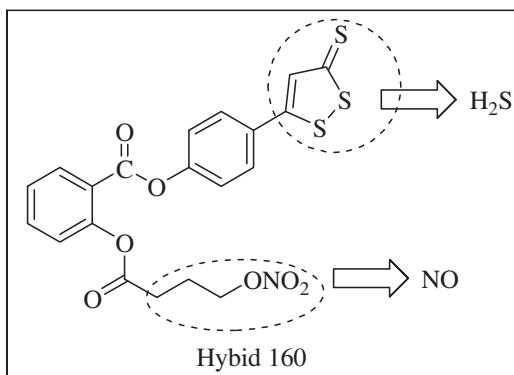
the researchers have previously shown enhances aspirin's cancer-fighting ability [534].

### 3. Conclusion

This review article presents the rational approaches behind the design of anticancer agents employing molecular hybridization as a tool for drug design. The literature survey clearly indicates the promising attributes of this technique as several new chemical architectures have been discovered from the fusion of pharmacophoric sub-units of known prototypes, resulting in more potent and selective hybrid molecules. Particularly in case of a physiopathology for which only few commercial drugs are available, this technique providing new molecular scaffolds by linking two moieties can be of immense importance. Overall, the scope of molecular hybridization is quite broad as it can result in compounds with modified selectivity profile, different and/or dual modes of action and reduced side effects. There is no doubt that targeting a single receptor/enzyme/protein is the primary strategy for the medicinal chemist but it is also assumed that the single target approach is basically the reason for the lack of successful treatment of multifactorial, complex diseases such as cancer. Although the strategies discussed in this compilation clearly highlights the interesting and promising anticancer profile of the hybrid structures, there are



**Fig. 93.** Structure of Aspirin-NO hybrid and benzyl nitrate.

**Fig. 94.** Mechanism of QM formation for benzyl nitrates.**Fig. 95.** Hybrid of aspirin releasing H<sub>2</sub>S and NO.

some limitations associated with these hybrid drugs which poses some serious challenges to the chemist such as high lipophilicity and chemical stability of the hybrids. In order to avoid incompatibilities, the functionalities selected for the fusion must be subjected to preliminary combination therapy. The hybrids designed by the fusion of chemical entities must outshine the cell killing potential of the individual functionalities and should also outweigh the disadvantages (compromised dose flexibility and schedule flexibility). Molecular hybridization as a tool has been particularly exploited for targeting tubulin exemplified through the number of research papers as microtubules represent one of the most logical targets for chemotherapy playing critical role in a number of cellular functions, such as chromosome segregation during cell division, intracellular transport, cell motility, and the maintenance of cell shape. The microtubule inhibitors such as taxol, colchicine, chalcones, and combretastatin, phenstatins and vinca alkaloids have been utilized as one of the functionality of the hybrids and promising results have been obtained in most of the cases with some of the tubulin based hybrids exhibiting anticancer activity at nanomolar level. Linkage with steroids as biological carrier vector for anticancer drugs and the inclusion of pyrrolo [2,1-c] [1,4] benzodiazepines (PBDs), a family of DNA interactive antitumor antibiotics derived from Streptomyces species in hybrid structure based drug design has also emerged as a potential strategy. Various heteroaryl based hybrids in particular isatin and coumarins have

also been designed and reported to possess remarkable inhibitory potential.

### Conflict of interest

The authors declare no conflict of interest.

### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.ejmech.2014.03.018>.

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