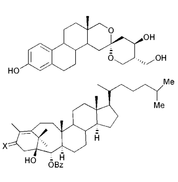
# Hybrid systems through natural product leads: An approach towards new molecular entities



**Goverdhan Mehta*[a] and Vishwakarma Singh*[b]**

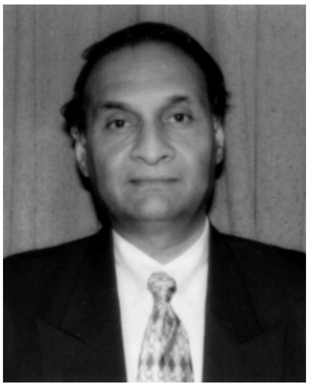
[a] *Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India.*
*E-mail: gm@orgchem.iisc.ernet.in*
[b] *Department of Chemistry, Indian Institute of Technology, Bombay, Mumbai 400 076, India.*
*E-mail: vks@chem.iitb.ac.in*

*Received 18th June 2002*
*First published as an Advance Article on the web 3rd October 2002*

**Hybrid systems are constructs of different molecular entities, natural or unnatural, to generate functional molecules in which the characteristics of various components are modulated, amplified or give rise to entirely new properties. These hybrids can be designed from carefully selected components either through domain integration of key structural/ functional features or *via* straightforward covalent linkages. Some of the recently reported hybrid systems based on steroid, carbohydrate, $C_{60}$-fullerene platforms, amongst others, mainly crafted with the object of enhancement of the therapeutical spectrum, will be discussed.**

## 1 Introduction

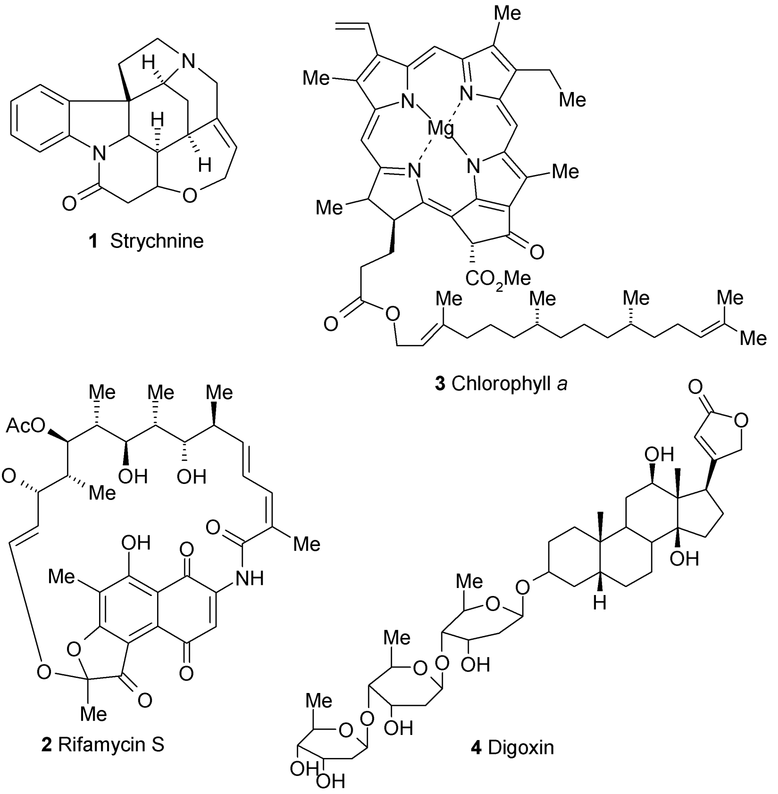
One of the main goals of organic synthesis from its very inception has been the search for new compounds that exhibit novel physical, chemical and biological properties.[1] In this quest, human intuition and leads from Nature have played a pivotal role. Nature makes natural products of bewildering diversity and complexity and these are generally derived through specific biosynthetic pathways like, shikimate, polyketide or mevalonate, leading to a particular class of compounds.[2] Many biologically active natural products are also derived through mixed biosynthesis. This may involve either integration of the different biosynthetic pathways to generate complex, enmeshed structures or eventuate in straightforward covalent linkage between components derived through different pathways. Examples of the former type are the complex indole alkaloids, *e.g.* strychnine **1**, which are derived from amino acid tryptophan and monoterpenic precursor loganin and ansa antibiotics like rifamycins **2** wherein the aromatic core is shikimate derived while the ansa chain is polyketide based.[2] On the other hand, glycoproteins, chlorophyll **3**, vitamin-$B_{12}$ and flavanoid and steroidal glycosides such as **4** (Fig. 1), to name a few, are well known examples of natural products in which various segments of the molecule have different biosynthetic origin but are linked covalently into a wholesome functional entity. Many of the natural products arising through such mixed biosynthesis have been found to exhibit unusual properties and biological activity as the different molecular segments act cooperatively to control and modulate conformation, recognition, communication, transport and solubility among other properties. These promising attributes of molecules of mixed biosynthetic origin perhaps led to the idea of generating novel molecular entities by rationally combining two or more different classes of compounds of natural or synthetic origin. The underlying expectation being that combination of structural features of two or more functionally active substances into one molecule or their covalent coupling may either enhance or modulate the desired characteristics of individual components or lead to new types of properties. An appealing feature of this approach is that it may provide myriad possibilities for generating a diverse array of new types of molecules for application in biology and material science. During the past two decades design of such entities has been receiving increasing attention and these have been referred to in the literature as 'hybrid molecules' or 'conjugates' or 'chimeras' or even 'mermaids'. Although, in strict terms 'hybrid molecules' refers to structural motifs derived through domain integration of two entities, in this review it has been used in an all inclusive sense



*Goverdhan Mehta has held Professorial Chairs at the University of Hyderabad (1977–1998) and the Indian Institute of Science, Bangalore (1998–present). Mehta's current research interest encompasses total synthesis of natural products, design of aesthetically pleasing molecular entities, probing stereogenesis and photodynamic therapy of cancer.*

*Vishwakarma Singh is Professor of Chemistry at the Indian Institute of Technology, Bombay. He also worked as a Group Leader at the Malti-Chem Research Centre Nandesari, Baroda (1982–84) and the Department of Chemistry, M. S. University of Baroda (1984–89) before joining IIT Bombay. His current research interests include development of new synthetic methodology, organic photochemistry, and total synthesis of complex natural products.*

DOI: 10.1039/b204748a


**1** Strychnine

**2** Rifamycin S

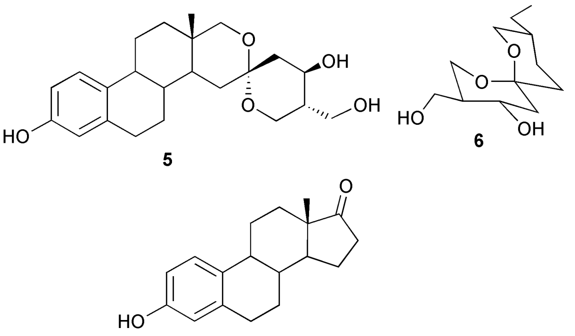
**3** Chlorophyll *a*

**4** Digoxin

**Fig. 1**

and covers entities derived either through integration of structural features or through covalent linkage of two or more natural/unnatural products. Although the examples of hybrid molecules are plenty, herein we wish to highlight some of the recently crafted systems which have been devised to either amplify certain characteristics, particularly the therapeutic spectrum based on natural product leads, or to probe intricate biochemical mechanisms. The selected examples discussed here are based on the well-known building platforms like steroids and $C_{60}$-fullerene and involve incorporation of functional entities like enediyne, nucleic acids, carbohydrates and porphyrin moieties. Synthesis of such entities can either involve intricate synthetic manipulations for structural integration or simple, straightforward connectivity through functional groups. Access to molecular hybrids through gene manipulations and combinatorial biosynthesis is also under investigation but will not be covered in this presentation.[3] Organic–inorganic hybrid systems which have been receiving a great deal of attention in recent years as novel materials are also not discussed here.

## 2 Hybrids based on steroid framework

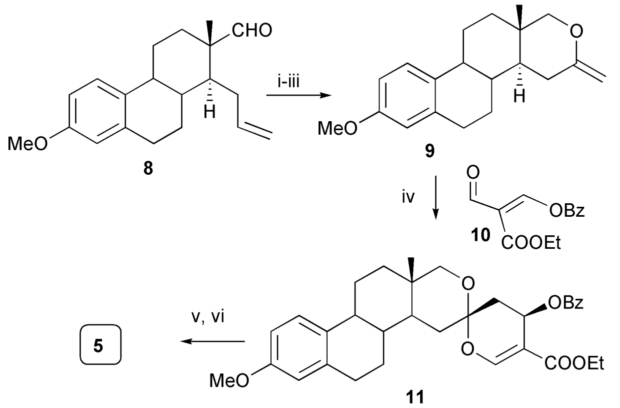

**5**

**6**

**7**

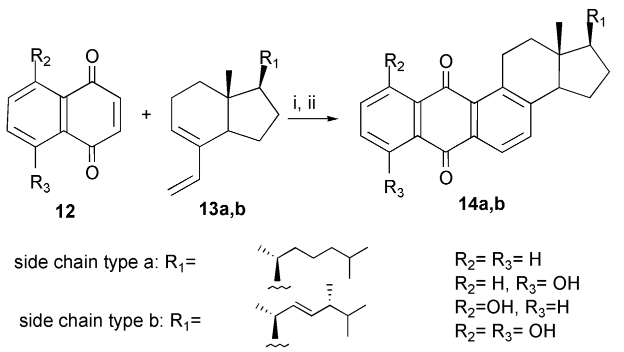
**Fig. 2**

Steroids on account of their wide occurrence, particularly among mammalian tissue, rigid framework with varying levels of functionalisation, broad biological activity profile and ability to penetrate the cell membrane and bind to specific hormonal receptors have found favor as building platforms for hybrid systems. Several molecular hybrids derived from diverse steroids through integration and/or linkage with other biomolecules, drugs and other functional molecules have been reported and a few notable examples will be discussed here. In an effort to design a new class of cytotoxic agents, Tietze and coworkers conceived of integrating the structural features of a highly active mycotoxin (−)-talaromycin B **6** with the hormone estrone **7** to devise a novel entity **5** (Fig. 2).[4] Towards this end, aldehyde **8** was obtained through the modification of ring D of estrone. Reduction in **8** followed by iodoetherification and elimination of HI furnished the tetracyclic derivative **9**. Hetero Diels–Alder reaction between **9** and **10** generated the required spiroacetal **11** which was elaborated to the hybrid system **5** (Scheme 1). The cytotoxic activities of **5** and its precursor on human cancer cells (cell line A 549) was determined and found to be only slightly lower than that of aldophosphamide.

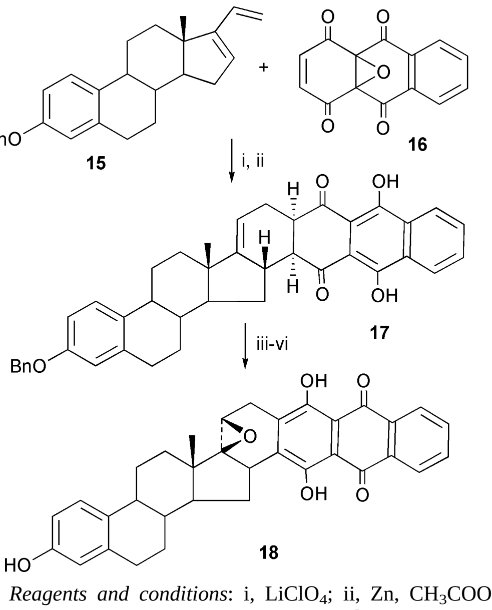


**Scheme 1** *Reagents and conditions*: i, $NaBH_4$, ii, $I_2$, $NaHCO_3$; iii, DBU; iv, **10**; v, DIBAH; vi, $PtO_2$, $H_2$, 50 bar.

Recognizing the importance of the anthraquinone subunit in many biologically active natural products, and anticancer agents like anthracyclines, De Riccardis and co-workers have crafted steroid–anthraquinone hybrids **14**[5] and estrogen–anthracenedione[6] hybrids **18**. While the CD rings of the steroid framework are retained in the case of the former, the entire ABCD ring framework is fused with the anthraquinone moiety in **18**. Synthesis of steroid–anthraquinone hybrid **14** is outlined in Scheme 2 and involves a Diels–Alder reaction between vitamin $D_3$ derived dienes **13** and naphthoquinones **12** as the key step. On evaluation of cytotoxic activity, these hybrids showed promising results.[5] The estrogen–anthracenedione hybrid **18** (estrarubicin) was also accessed through a Diels–Alder approach in which diene **15** derived from estrone was reacted with the dienophile **16** to furnish **17**. Subsequent transformations led to estrarubicin **18** having structural integration of the steroid and anthracycline-like moieties with an additional electrophilic epoxide ring, Scheme 3.

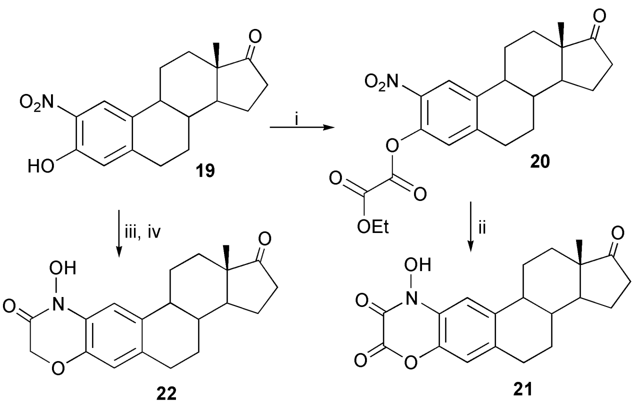


**Scheme 2** *Reagents and conditions*: i, heat; ii, DBU, $O_2$.



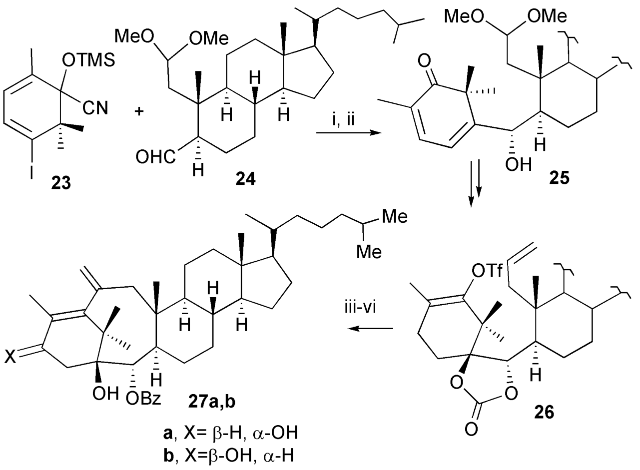
**Scheme 3** *Reagents and conditions*: i, $LiClO_4$; ii, Zn, $CH_3COOH$; iii, $Pb(OAc)_4$, $CH_3COOH$; iv, $Et_3N$; v, *m*-CPBA; vi, Pd/C, $H_2$.

Taking a clue from the observation that the benzoxazine subunit is present in many natural products that exhibit promising phytotoxicity, Schonecker and co-workers[7] have devised estrone–cyclic-hydroxamic acid hybrids **21** and **22** from nitroestrone **19** as shown in Scheme 4.



**Scheme 4** *Reagents and conditions*: i, $EtOCOCOCl$, $Et_3N$; ii, Pt(S)/C–$H_2$, AcOH; iii, $BrCH_2COOEt$, $K_2CO_3$; iv, Zn, $NH_4Cl$.

In view of the important role of baccatin III and related taxoids in cancer chemotherapy, Danishefsky's group[8] conceived and developed a route to baccatin III–cholesterol hybrid **27** in which the steroid A ring was elaborated to taxoid B ring. Intramolecular Heck reaction in the precursor **26** leading to the AB ring of taxane is the key element in this approach. The intermediate **26** containing BCD rings of steroid was assembled through the addition of the iododiene **23** to the aldehyde **24** derived from cholesterol, and subsequent manipulation of the resulting intermediate **25**, Scheme 5.

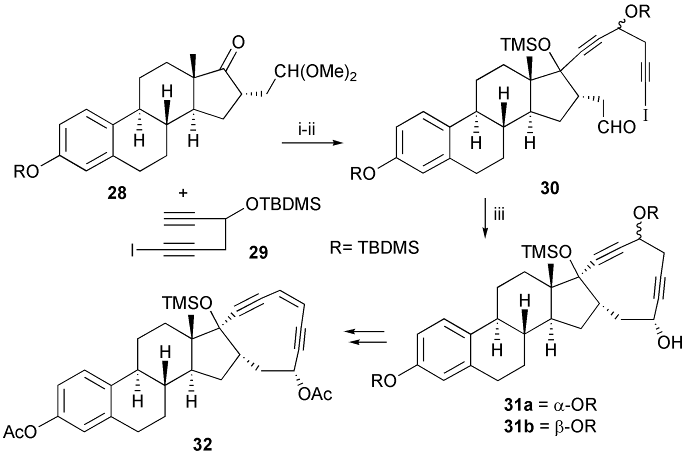


**Scheme 5** *Reagents and conditions*: i, $^{t}$BuLi; ii, $^{t}Bu_4NF$; iii, $[Pd(PPh_3)_4]$, $K_2CO_3$; iv, PhLi; v, PDC, $^{t}$BuOOH; vi, $NaBH_4$, $CeCl_3$.

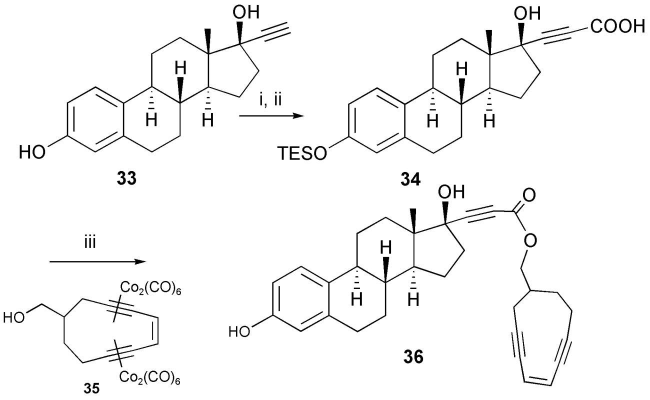
The exceptional promise of the enediyne moiety to effect DNA cleavage through 1,4-diyl generated through Bergman cycloaromatization and the discovery of several naturally occurring cytotoxic agents like neocarzinostatin, the esperamycin–calicheamicin group and dynemicin bearing this moiety inspired Wang and Clercq[9] to design estramycin **32**, a novel steroid based hybrid. The expectation was that the chemotherapeutic activity against hormone responsive tumors could be enhanced through linkage with a steroid hormone. An enediyne functionality was installed on the ring D of estrone through addition of iododiyne **29** to the ketone **28** (readily available from estrone) to give **30** which upon Nozaki coupling furnished **31** along with other diastereomers and was then converted into the hybrid **32**, Scheme 6.

Jones and co-workers[10] have devised a new estramycin in which the enediyne moiety is linked to the 17-position of the hormone estradiol. Synthesis of the enediyne-estradiol hybrid **36** was achieved from estrone derivatives **33** and **34**, Scheme 7. Coupling with diyne alcohol **35** led to estramycin **36** a promising lead compound which exhibited inhibition of estrogen-induced transcription in T47-D human breast cancer cells.

The ansa antibiotic geldanamycin (GDM) **37** (Fig. 3) is not only a potent inhibitor of src kinase but also binds to the Hsp90 chaperone protein and causes the degradation of several signaling proteins. In order to achieve selective degradation of particular proteins for therapeutic applications, Danishefsky



**Scheme 6** *Reagents and conditions*: i, $LiN(TMS)_2$; ii, TMSOTf; iii, $CrCl_2$, $NiCl_2$.



**Scheme 7** *Reagents and conditions*: i, TESCl, 94%; ii, ${}^{n}$BuLi, $CO_2$, 69%; iii, 1-ethyl-3-(3-dimethylaminopropyl)-carbodimide (EDCl), then TBAF, 78%.

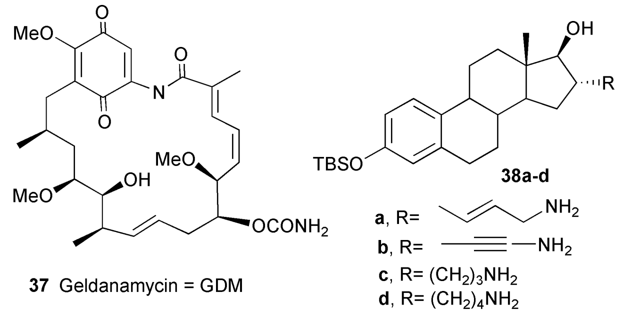
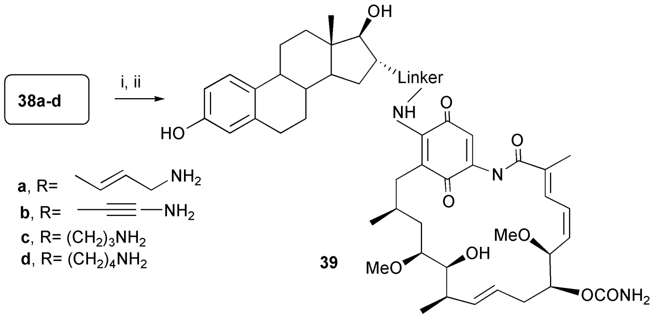


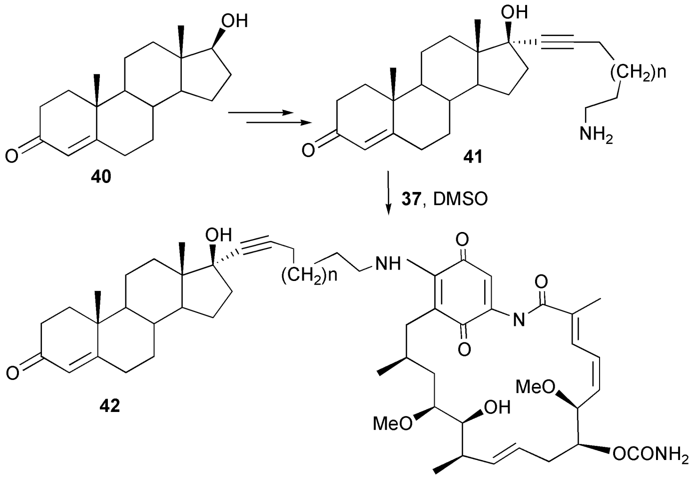
**Fig. 3**

and co-workers have prepared hybrids **39** and **42** of geldanamycin with estradiol and testosterone, respectively.[11] Michael addition of the amines **38a–d** derived from estrone to GDM gave the hybrids **39a–d** with subtle variation in the tether, Scheme 8. These hybrids were found to be active in MCF7 breast cancer cells and more selective than the parent causing the degradation of ER and HER2 but not of other GDM targets. Similarly, the male hormone testosterone **40** was elaborated into amines **41** and linked to GDM to furnish hybrids **42**, Scheme 9.[12]

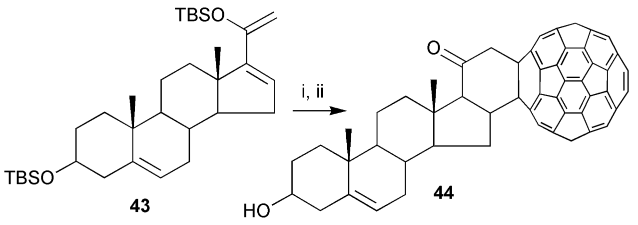
A steroid–fullerene hybrid **44** has been prepared and its cytotoxic effects at subcellular and cellular level examined.[13] Union of $C_{60}$-fullerene with steroid framework was effected through a Diels–Alder cycloaddition with the diene **43** to furnish the fullerene–steroid hybrid **44**, Scheme 10. Preliminary assay indicated that the hybrid **44** can inhibit the reconstituted SR $Ca^{2+}$-ATPase and affect the survival of $A_{549}$ cells.



**Scheme 8** *Reagents and conditions*: i, Geldanamycin, DMSO; ii, TBAF–HOAc.



**Scheme 9**



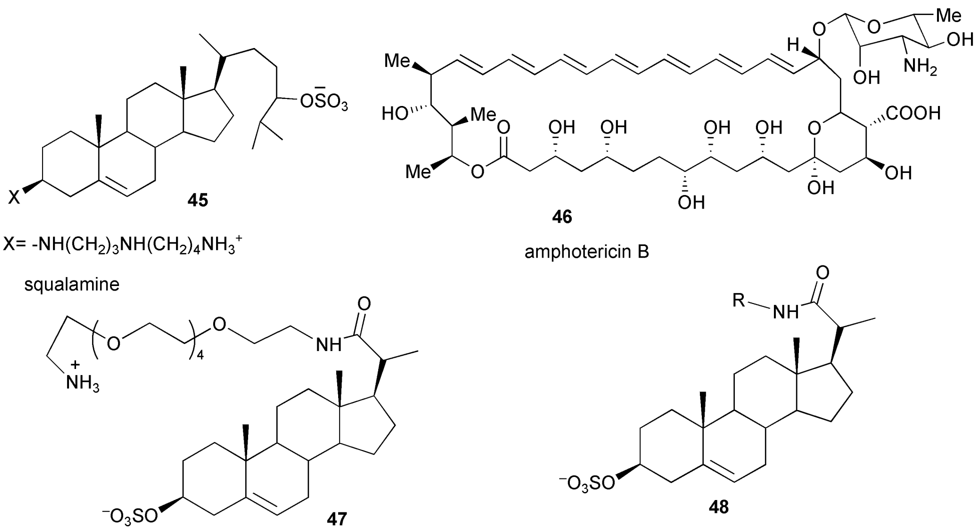
**Scheme 10** *Reagents and conditions*: i, $C_{60}$, Δ; ii, *p*-TsOH, Δ.

Regen and his associates[14] designed novel constructs **47** and **48** (Fig. 4) which are endowed with features reminiscent of amphotericin B **46**, an antibiotic which is known to form pores in lipid bilayers, and a marine natural product squalamine **45**, a sterol–spermidine conjugate. The effort was motivated by the desire for antimicrobial activity against a broad spectrum of microorganisms. Interestingly **48** exhibits antimicrobial properties similar to squalamine **45**; the polyether **47** was found to be inactive.

The potential of photo-dynamic therapy (PDT) as a promising non-invasive protocol against cancer has stimulated interest in cholic acid–porphyrin, estrone–porphyrin and deoxycholic acid–porphyrin–anthraquinone triads to combine a sensitizer with a recognition element (bile acids, female sex hormones) and an intercalating agent (anthraquinone). The derived hybrids **49**, **50**[15] and **51**[16] (Fig. 5) exhibit nuclease activity.

## 3 Hybrids based on taxoids, anthracyclines and β-lactams

As mentioned earlier, enhancement and fine-tuning the efficacy of drugs was a major motivation for the design of hybrid



**45**

X= $-NH(CH_2)_3NH(CH_2)_4NH_3^+$

squalamine

**46**

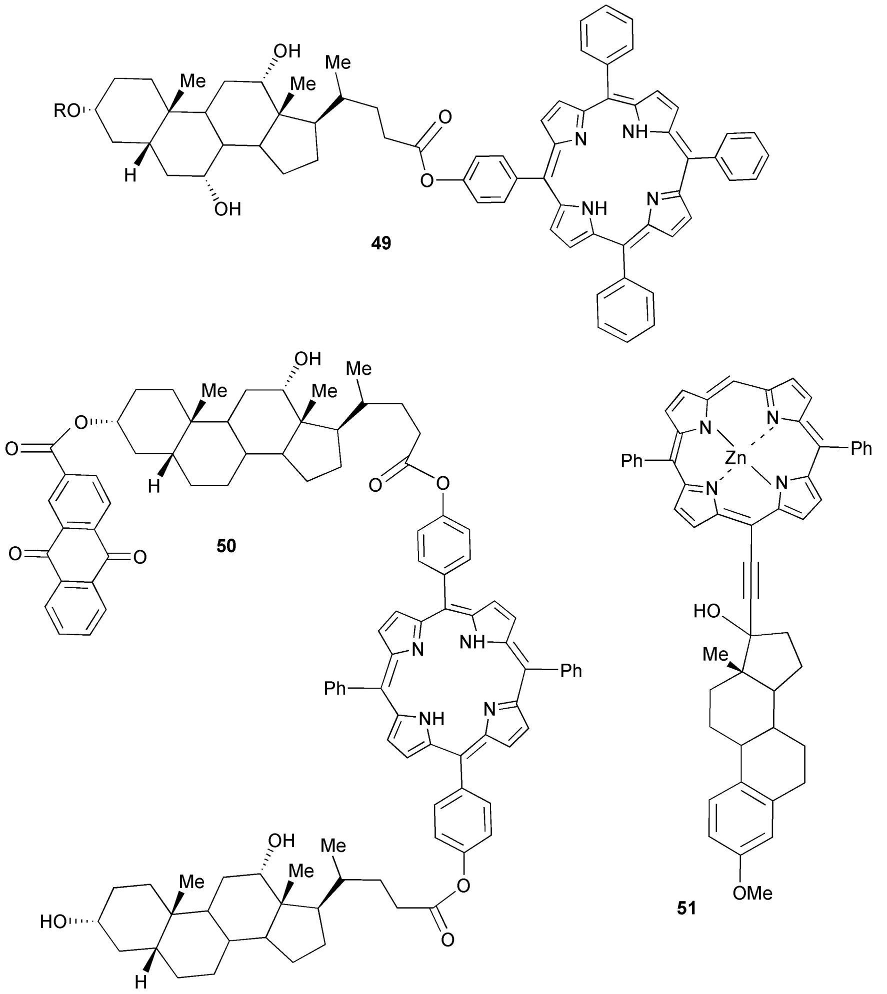
amphotericin B

**47**

**48**

R= $-(CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_3^+$

**Fig. 4**



**49**

**50**

**51**

**Fig. 5**

systems. Taxoids and anthracyclines represent two groups of natural products, based on which several anti-cancer drugs are in clinical use and it was a natural impulse of synthetic and medicinal chemists to devise hybrids based on them.

Fallis and co-workers[17] designed taxamycins **53** and **54** which contain ring A of taxol **52** and an enediyne moiety connected through a bridge, Fig. 6. It was expected that both tubulin binding and cycloaromatization would operate in concordant manner and induce cancer cell damage. However, these hybrid compounds were weaker than taxol in influencing tubulin dynamics and their cytotoxic activity against HT-29 cancer cell lines was also weak.

Research groups of Kingston[18] and Ojima[19] have reported several paclitaxel–macrocyclic constructs of which **55** and **56** (Fig. 7) are typical examples with the latter somewhat remotely combining the structural features of taxoids with the well-known cytotoxic agent epothilone. While these hybrids largely retained the cytotoxicity of paclitaxel when evaluated against human cancer cell lines, their tubulin binding ability was diminished.

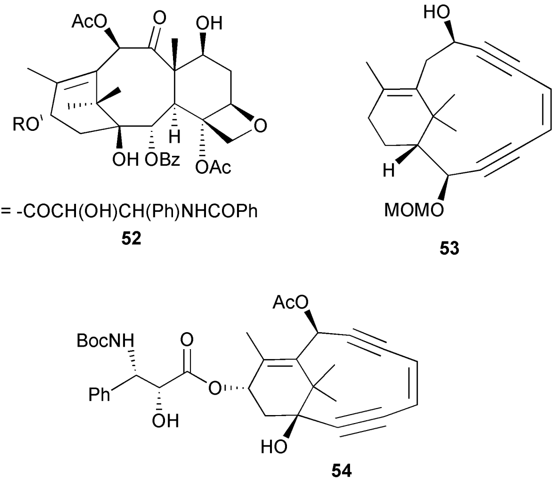


**Fig. 6**

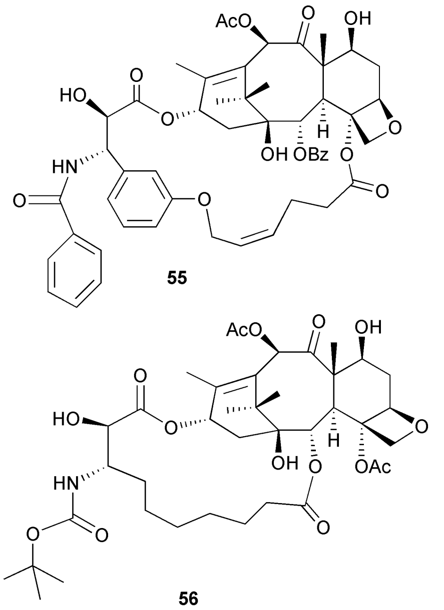
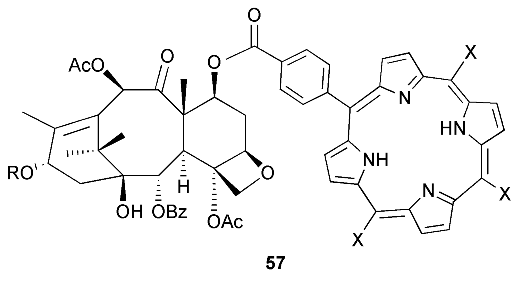


**Fig. 7**

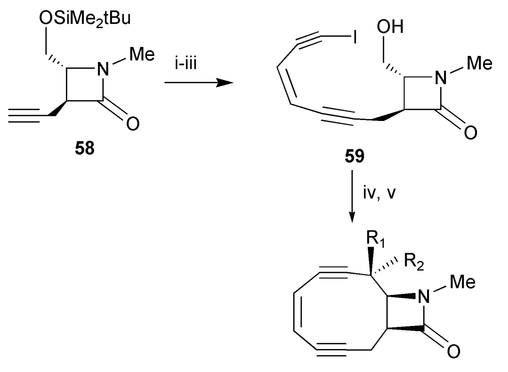
In another approach to amplify the anti-cancer potency of taxol **52**, it has been linked with a porphyrin moiety through the pharmacophorically benign C7 position to furnish hybrid **57** (Fig. 8). The idea was to complement the cytotoxic activity with photodynamic action through light activation of the porphyrin, a sort of dark and light therapy, to provide double lethal attack against tumors.[20]



**57**

**Fig. 8**

β-Lactam antibiotics have been in extensive use for over half century but the persistent problem of drug resistance continues to demand development of newer and potent variations. Banfi and Guanti[21] devised lactendiynes **61** in which a β-lactam ring is fused to the 10-membered enediyne ring, Scheme 11. The β-lactam **58** was transformed into **59** containing an enediyne group. Oxidation and intramolecular Nozaki coupling led to hybrid **60** along with its diastereoisomer. Several derivatives of **60** were prepared and one of them, the methyl ether **61** was shown to undergo cycloaromatization indicating the intervention of a 1,4-diyl species.



**60a**, $R_1$= OH, $R_2$= H
**60b**, $R_1$=H, $R_2$= OH
**61 a**, $R_1$= OMe, $R_2$= H
**61b**, $R_1$= H, $R_2$= OMe

**Scheme 11** *Reagents and conditions*: i, $Me_3SiCCCH{=}CHCl$, CuI, $[(PhCN)_2PdCl_2]$, piperidine; ii, $AgNO_3$, NIS; iii, HF, $H_2O$; iv, $(COCl)_2$, DMSO, $Et_3N$; v, $CrCl_2$, $NiCl_2$.

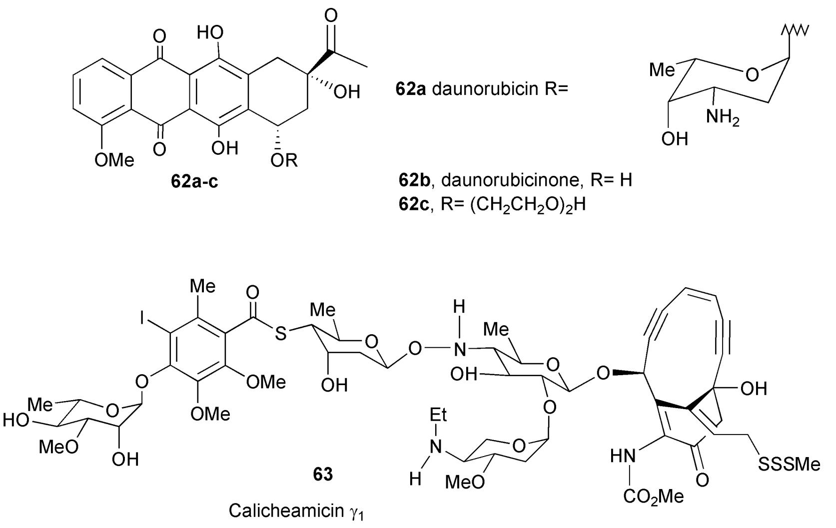
Danishefsky and co-workers have synthesized novel hybrids by swapping the carbohydrate domain of two powerful anti-cancer agents, the clinically used daunorubicin **62a** and calicheamicin $\gamma_1$ **63** (Fig. 9). Thus, daunorubicinone **62b**, aglycon of **62a** was glycosidated with the carbohydrate segment of calicheamicins to furnish the hybrid species calichearubicins **65**, Scheme 12.[22] The objective **65**, was reached through the glycosidation of the protected trichloroacetamidate **64** in the presence of AgOTf followed by deprotection to calichearubicin A **65**, Scheme 12. Similarly, calichearubicin B **66** was synthesized *via* coupling of tethered daunorubicinone **62c** and **64** followed by removal of protecting groups, Scheme 13. Interaction of both **65** and **66** with DNA was studied and it was observed that in the tethered hybrid **66**, the anthracycline moiety exhibits marked propensity towards intercalation. DNA foot printing experiments with **65** and **66** led to the surmise that the latter combines the unique specificities of its two components.

## 4 Hybrids based on duocarmycin and CC-1065

Duocarmycin **67** and CC-1065 **68** (Fig. 10) are a new class of potent cytotoxic agents that alkylate DNA. In order to enhance the therapeutic potential of these molecules efforts have been made to combine their DNA alkylating structural part with a moiety capable of sequence specific recognition. Consequently, several groups have reported efforts in which the active pharmocophoric segment of **67** and **68** has been linked to the pyrrole or imidazole amide units present in lexitropsins, well known for sequence specific recognition.

Groups of Shishido and Shibuya have developed hybrids **72a**,**b** containing indoline unit, a precursor of the pharmacophore moiety present in CC 1065 and duocarmycins, and pyrrole amides, present in DNA minor groove binding lexitropsins, Scheme 14.[23] It is interesting to note that hybrid **72a** having unnatural configuration was more potent than **72b** with natural configuration in DNA cleavage activity. The unnatural hybrid **72a** also exhibited DNA alkylation selectivity for the A-T rich region.

In another approach Saito and co-workers[24] synthesized hybrids **76** that contain segments of duocarmycin A and pyrrole/



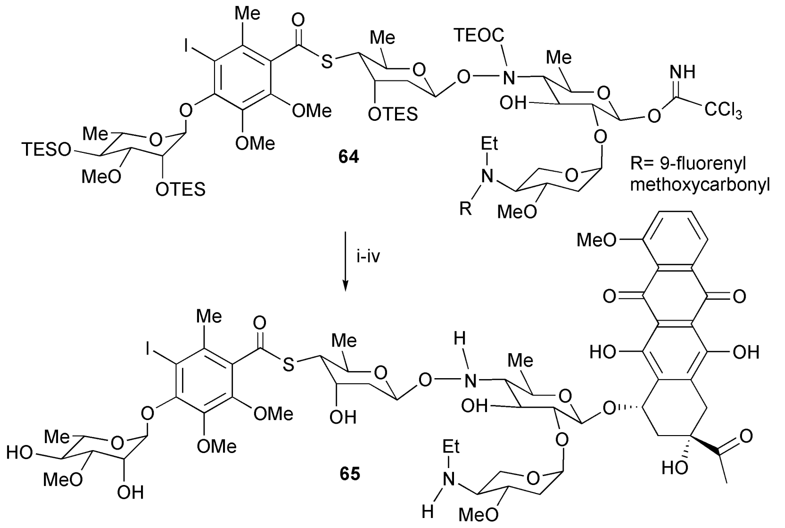
**62a-c**

**62a** daunorubicin R=

**62b**, daunorubicinone, R= H
**62c**, R= $(CH_2CH_2O)_2H$

**63**
Calicheamicin $\gamma_1$

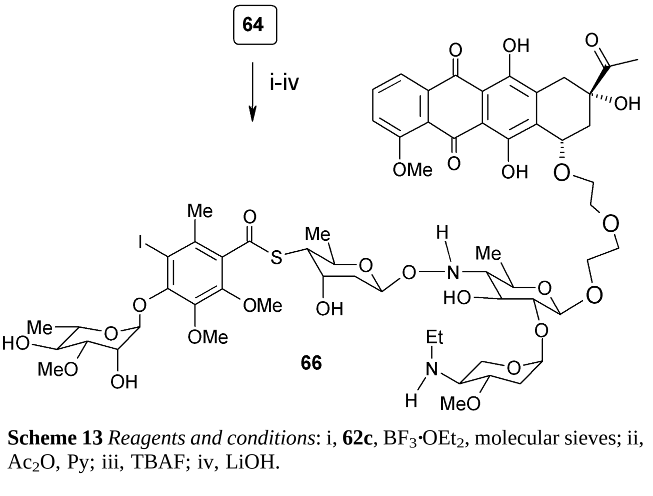
**Fig. 9**



**64**

**65**

**Scheme 12** *Reagents and conditions*: i, **62b**, AgOTf, molecular sieves; ii, $Ac_2O$, Py; iii, TBAF; iv, LiOH.



**66**

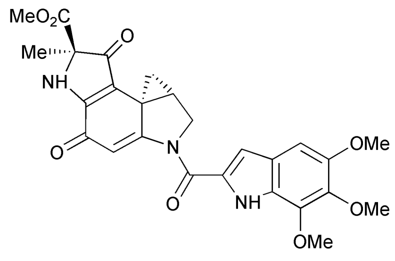
**Scheme 13** *Reagents and conditions*: i, **62c**, $BF_3·OEt_2$, molecular sieves; ii, $Ac_2O$, Py; iii, TBAF; iv, LiOH.

imidazole amide segments of distamycin.[24] The pyrrole segment **74** was synthesized in several steps from **73** while the duocarmycin segment **75** was readily obtained from duocarmycin B2. Coupling of **74** with **75** furnished the desired hybrids **76**, Scheme 15. The results on DNA alkylation indicated that this is a promising approach for alkylating purine bases at the desired site.

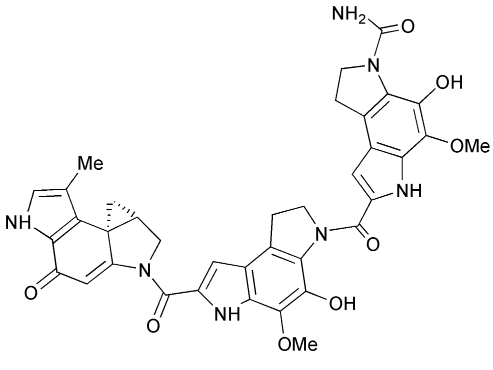
Tietze *et al.* have conceptualized hybrids **77** and **78** of indoline unit, a penultimate intermediate for the pharmacophore moiety present in CC 1065, and carbohydrates. Thus, the indoline derivative **80** was prepared from **79** *via* Heck reaction and hydroboration. Reaction of **80** with tetracetyl-α-D-galactosyltrichloroacetimidate **81** and further manipulations gave the pro-drug **77**, Scheme 16. The β-D-glucoside **78** was also synthesized along similar lines.[25] The hybrids **77** and **78** were evaluated for their toxicity against human bronchial carcinoma cell line A 549.

## 5 Hybrids based on $C_{60}$-fullerene

The discovery of $C_{60}$ and its unusual physico-chemical properties and reactivity has become a topic of interest in medicinal chemistry and material science. Compounds derived from $C_{60}$ have shown promising biological profile and efficacy in DNA photo-cleavage, HIV protease inhibition, neuroprotection and apoptosis. In order to harness these attributes and to improve cellular level uptake, delivery and recognition, many hybrids of $C_{60}$ with molecules possessing biological affinity like nucleic acids, proteins and carbohydrates have been prepared. An early example is of the $C_{60}$-netropsin related hybrid **82** (Fig. 11) to achieve DNA cleavage specificity.[26]

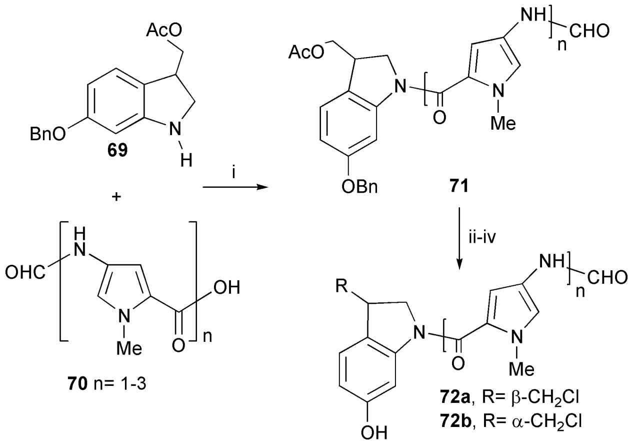


**67**(+)-Duocarmycin A

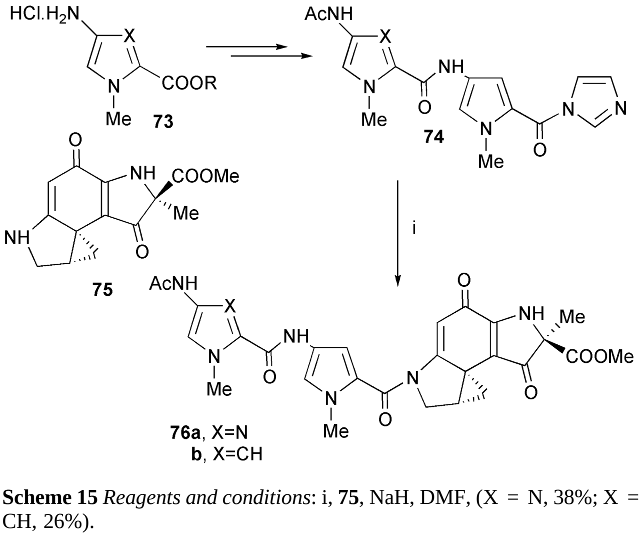


**68** (+)-CC-1065

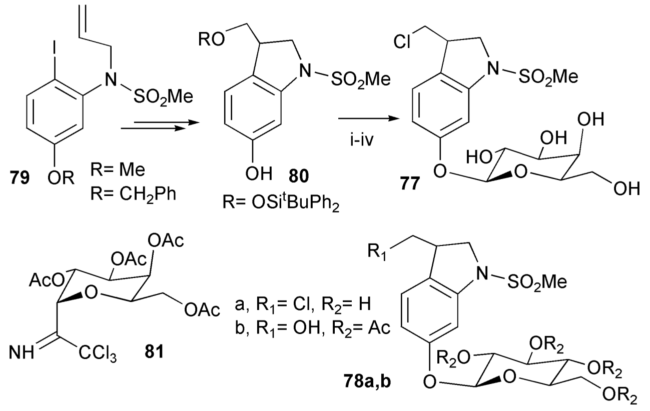
**Fig. 10**



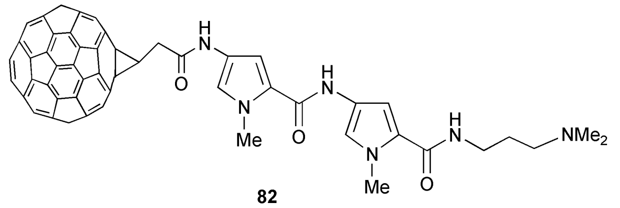
**Scheme 14** *Reagents and conditions*: i, EDCI·HCl; ii, LiOH·$H_2O$; iii, $Ph_3P$, $CCl_4$; iv, $BBr_3$.



**Scheme 15** *Reagents and conditions*: i, **75**, NaH, DMF, (X = N, 38%; X = CH, 26%).



**Scheme 16** *Reagents and conditions*: i, **81**, $BF_3$·$OEt_2$, molecular sieves; ii, TBAF, $SiO_2$; iii, $PPh_3$, $CCl_4$; iv, $K_2CO_3$, MeOH.



**82**

**Fig. 11**

Subsequently, several fullerene conjugates/hybrids for photodynamic therapy (PDT) and sequence specific DNA cleavage have been reported.[27] Rubin and co-workers[28] designed synthesis of $C_{60}$-linked deoxynucleotide (DHFDON-1) **83** (Fig. 12) and it interacted with light and oxygen to damage only guanosines in the single-stranded regions in DNA which are closest to $C_{60}$. Prato and co-workers[29] designed synthesis of a fullerene hybrid **84** (Fig. 12) containing a trimethoxyindole (TMI) moiety reminiscent of the minor groove binder duocarmycin and a oligonuclotide for achieving sequence selectivity. Several groups have been actively engaged in the synthesis of novel fullerene–porphyrin hybrids in which the fullerene and porphyrin moieties are coupled through a variety of linkers including a steroid **85** (Fig. 13).[30] These fullerene porphyrin hybrids were designed in the context of application in the PDT of cancer.

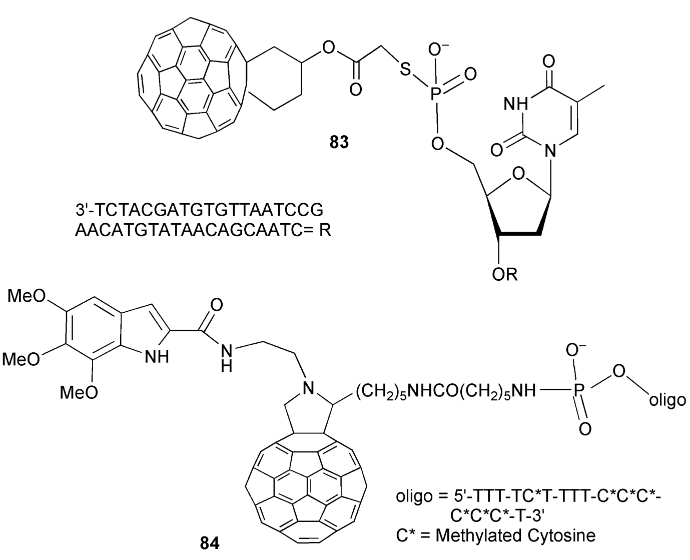


**Fig. 12**

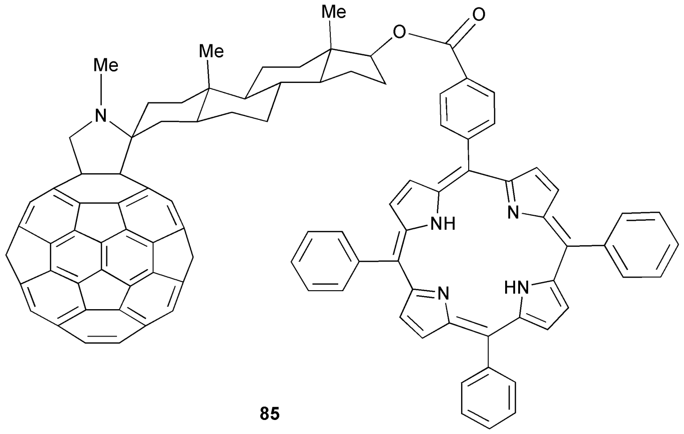
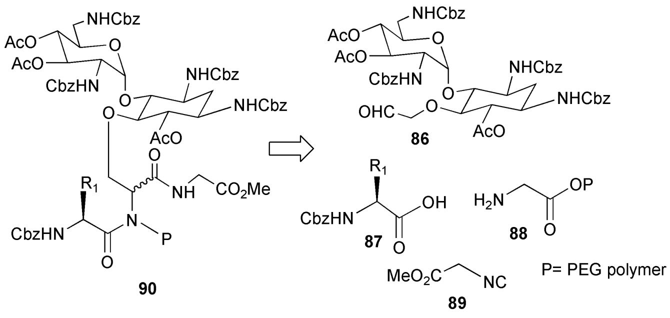


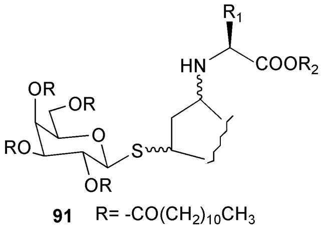
**Fig. 13**

## 6 Carbohydrate–peptide hybrids

Glycoconjugates, particularly glycoproteins, play an important role in various biological processes such as modulation of protein function, cell growth and differentiation and cell–cell communication. The oligosaccharide moiety present in the glycoproteins and glycolipids, presumably has a key role in their diverse biological functions. In view of this, there is a great deal of interest in the design of carbohydrate–peptide hybrids as glycopeptide mimics, and various strategies have been devised for this purpose. While Wong's group[31] has employed Ugi's multi-component approach to generate a library of neomycin mimetics **90** (Scheme 17), Nilsson *et al.*[32] have adopted a building block approach to prepare 1-thio-β-D-galactopyranoside–amino acid library **91** (Fig. 14) which was found to be a good inhibitor of β-galactosidase from *E. coli*.



**Scheme 17**



**91** R= $-CO(CH_2)_{10}CH_3$

**Fig. 14**

Carbohydrate–peptide derived oligomeric structures offer the possibility of controlling shape and conformation and such hybrid molecules may exhibit helical, hairpin and other secondary structures. Two examples **92** and **93** (Fig. 15) of carbopeptoid oligomeric structures from the groups of Fleet[33] and Chakraborty,[34] respectively, indicate emerging interest in such designs.

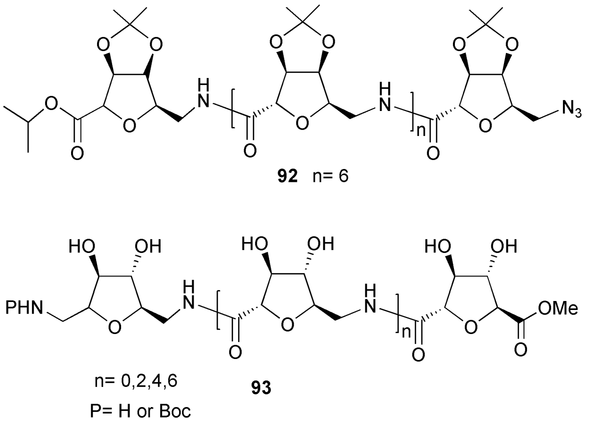
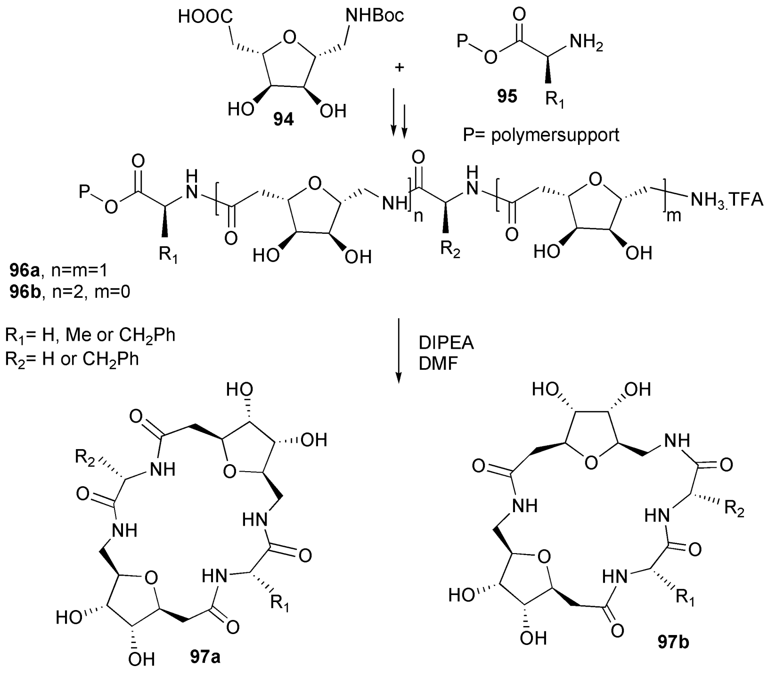


**Fig. 15**

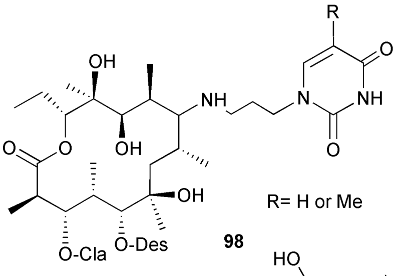
Van Boom[35] developed a parallel synthesis of cyclic sugar amino acid–amino acid hybrids **97a**, **b** as a new class of receptor molecules endowed with structural elements of cyclodextrins and cyclic peptides, Scheme 18.

Recently, hybrids based on a combination of macrolides and nucleobases/nucleosides such as **98**, **99** and their congeners



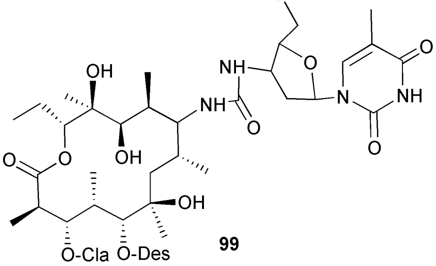
**Scheme 18**

were synthesized by Costa and Vilarrasa (Fig. 16).[36] However, their biological activities were not promising.



R= H or Me

**98**

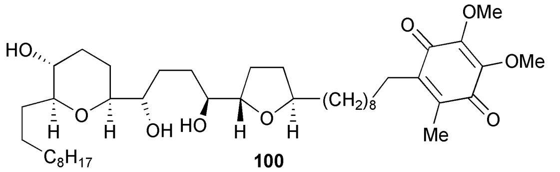


**99**

Fig. 16

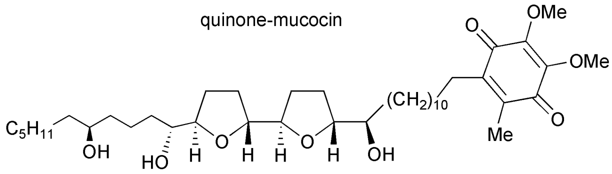
## 7 Miscellaneous hybrids

Koert *et al.* have described the synthesis of hybrids **100** and **101** (Fig. 17) that contain structural features of annonaceous acetogenins and ubiquinone with a view to design molecular probes for studies on mitochondrial complex I (NADH–ubiquinone oxidoreductase).[37] It was observed that the quinone–mucocin **100** and the related quinone–squamocin D **101** hybrids were much more potent inhibitors of mitochondrial complex I than mucocin.



**100**

quinone-mucocin

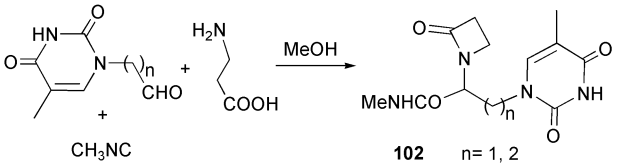


**101**

quinone-squamocin D

Fig. 17

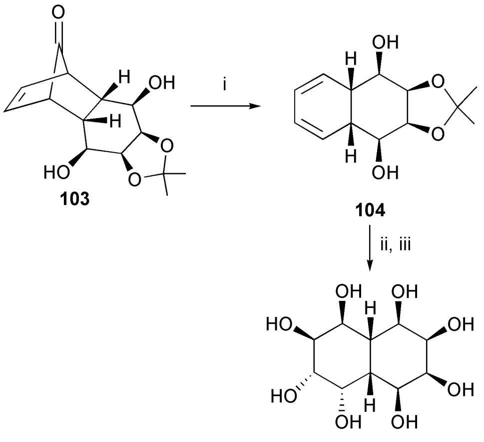
Ugi and co-workers[38] developed a synthetic route to compounds of type **102** in which a β-lactam moiety is attached to a nucleoside. The synthesis is based on multicomponent reaction (MCR) approach in which a β-amino acid, oxo-component and isocyanides react to form a β-lactam ring (Scheme 19).



**102** n= 1, 2

Scheme 19

In the context of the design of new polycyclitols for selective glycosidase inhibition, the synthesis of carbasugar hybrid **105** has been reported.[39] Thus, the readily available precursor **103** was converted *via* extrusion of CO to diene **104** and this was elaborated into the hybrid **105** through osmylation and deprotection of the acetonide moiety Scheme 20).



**103**

**104**

**105**

**Scheme 20** *Reagents and conditions*: i, $C_6H_5NO_2$, 160 °C; ii, $OsO_4$, NMMO; iii, 30% $CF_3COOH$.

## 8 Conclusion

As we have seen, the possibilities of generating hybrid systems for creating molecular diversity through either domain integration or covalent connection of two or more diverse entities are almost unlimited. The possibility of assembling large, nanoscopic, multi-component, multi-functional entities will continue to engage the attention of organic chemists. Natural products and leads emanating from them will be the bedrock of these efforts. Even the tools of combinatorial chemistry can be applied to yield libraries of hybrid molecules. However, precision crafting is necessary to generate the desired characteristics, particularly in the case of biologically active compounds and natural products, where significant modulation and/or enhancement of the therapeutic spectrum should be achievable. A good many of the recently reported efforts on the creation of hybrid systems have focused on cancer related chemotherapeutic drugs. However, with the availability of the three dimensional structures of many receptors and access to genome sequences, creation of new hybrid systems for these new targets is likely to receive increasing attention.

## 9 Acknowledgements

GM thanks JNCASR and VS is grateful to DST and CSIR New Delhi for continued research support. VS is also thankful to the Department of Organic Chemistry, Indian Institute of Science, Bangalore for a visiting fellowship and kind hospitality.

## 10 References

1 K. C. Nicolaou, D. Vourloumis, N. Winssinger and P. S. Baran, *Angew. Chem., Int. Ed.*, 2000, **39**, 44–122 and references cited therein.

2 (*a*) D. Ranganathan and S. Ranganathan, *Art in Biosynthesis*, Academic Press, New York, 1976, **vol. 1**; (*b*) H. Floss, *Nat. Prod. Rep.*, 1997, **14**, 433–452.

3 (*a*) R. McDaniel, A. Thamchaipenet, C. Gustafsson, H. Fu, M. Betlach, M. Betlach and G. Ashley, *Proc. Natl. Acad. Sci. U.S.A.*, 1999, **96**, 1846–1851; (*b*) R. Pieper, C. Kao, C. Khosla, G. Luo and D. E. Cane, *Chem. Soc. Rev.*, 1996, **25**, 297–302.

4 L. F. Tietze, G. Schneider, J. Wolfling, A. Fecher, T. Nobel, S. Petersen, I. Schuberth and C. Wulff, *Chem. Eur. J.*, 2000, **6**, 3755–3760 and references therein.

5 F. De Riccardis, I. Izzo, M. Di Filippo, G. Sodano, F. D′Acquisto and R. Carnuccio, *Tetrahedron*, 1997, **53**, 10871–10882.

6 F. De Riccardis, D. Meo, I. Izzo, M. Di Filippo and A. Casapullo, *Eur. J. Org. Chem.*, 1998, 1965–1970.

7 von I. Scherlitz-Hofmann, M. Dubs, R. Krieg, B. Schonecker, M. Kluge and D. Sicker, *Helv. Chim. Acta*, 1997, **80**, 2345–2351.

8 J. J. Masters, D. K. Jung, S. J. Danishefsky, L. B. Snyder, T. K. Park, R. C. A. Issacs, C. A. Alaimo and W. B. Young, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 452–455.

9 J. Wang and P. J. De Clercq, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 1749–1752.

10 G. B. Jones, G. Hynd, J. M. Wright, A. Purohit, G. W. Plourde II, R. S. Huber, J. E. Mathews, A. Li, M. W. Kilgore, G. J. Bubley, M. Yanacisin and M. A. Brown, *J. Org. Chem.*, 2001, **66**, 3688–3695.

11 S. D. Kuduk, F. F. Zheng, L. Sepp-Lorenzino, N. Rosen and S. J. Danishefsky, *Bio-Org. Med. Chem. Lett.*, 1999, **9**, 1233–1238.

12 S. D. Kuduk, C. R. Harris, F. F. Zheng, L. Sepp-Lorenzino, Q. Ouerfelli, N. Rosen and S. J. Danishefsky, *Bio-Org. Med. Chem. Lett.*, 2000, **10**, 1303–1306.

13 L.-S. Li, Y.-J. Hu, Y. Wu, Y.-L. Wu, J. Yue and F. Yang, *J. Chem. Soc., Perkin Trans. 1*, 2001, 617–621.

14 A. Sadownik, G. Deng, V. Janout and S. L. Regen, *J. Am. Chem. Soc.*, 1995, **117**, 6138–6139.

15 G. Mehta, S. Muthusamy, B. G. Maiya and M. Sirish, *J. Chem. Soc., Perkin Trans. 1*, 1996, 2421–2423.

16 E. D. Sternberg, D. Dolphin and C. Bruckner, *Tetrahedron*, 1998, **54**, 4151–4202 and references therein.

17 (*a*) Y.-F. Lu, C. W. Harwig and A. G. Fallis, *J. Org. Chem.*, 1993, **58**, 4202–4204; (*b*) S. Py, C. W. Harwig, S. Banerjee, D. L. Brown and A. G. Fallis, *Tetrahedron Lett.*, 1998, **39**, 6139–6142.

18 B. B. Metaferia, J. Hoch, T. E. Glass, S. L. Bane, S. K. Chatterjee, J. P. Snyder, A. Lakdawala, B. Cornett and D. G. I. Kingston, *Org. Lett.*, 2001, **3**, 2461–2464.

19 I. Ojima, S. Lin, T. Inoue, M. L. Miller, C. P. Borella, X. Geng and J. J. Walsh, *J. Am. Chem. Soc.*, 2000, **122**, 5343–5353.

20 G. Mehta, B. G. Maiya, S. Muthusamy, M. Chanon and M. Julliard, French Patent application (demand No.9807228).

21 L. Banfi and G. Guanti, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2393–2395.

22 K. M. Depew, S. M. Zeman, S. H. Boyer, D. J. Denhart, N. Ikemoto, S. J. Danishefsky and D. M. Crothers, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2797–2801.

23 K. Shishido, S. Haruna, C. Yamamura, H. Iitsuka, H. Nemoto, Y. Shinohara and M. Shibuya, *Bio-Org. Med. Chem. Lett.*, 1997, **7**, 2617–2622.

24 Z.-F. Tao, T. Fuziwara, I. Saito and H. Sugiyama, *Angew. Chem., Int. Ed.*, 1999, **38**, 650–653.

25 L. F. Tietze, R. Hannemann, W. Buhr, M. Logers, P. Menningen, M. Lieb, D. Starck, T. Grote, A. Doring and I. Schuberth, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2674–2676.

26 E. Nakamura, H. Tokuyama, S. Yamago, T. Shiraki and Y. Sugiura, *Bull. Chem. Soc. Jpn.*, 1996, **69**, 2143–2151.

27 S. Boutorine, H. Tokuyama, M. Takasugi, H. Isobe, E. Nakamura and C. Helene, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 2462–2465 and references therein.

28 Y.-Z. An, C. B. Chen, J. L. Anderson, D. S. Sigman, C. S. Foote and Y. Rubin, *Tetrahedron*, 1996, **52**, 5179–5189.

29 M. Bergamin, T. Da Ros, G. Spalluto, A. Boutorine and M. Prato, *Chem. Commun.*, 2001, 17–18.

30 S. MacMahon, R. Fong II, P. S. Baran, I. Safonov, S. R. Wilson and D. I. Schuster, *J. Org. Chem.*, 2001, **66**, 5449–5455.

31 W. K. C. Park, M. Auer, H. Jaksche and C.-H. Wong, *J. Am. Chem. Soc.*, 1996, **118**, 10150–10155.

32 U. J. Nilsson, E. J.-L. Fournier and O. Hindsgaul, *Bioorg. Med. Chem.*, 1998, **6**, 1563–1575.

33 T. D. W. Claridge, D. D. Long, N. L. Hungerford, R. T. Aplin, M. D. Smith, D. G. Marquess and G. W. J. Fleet, *Tetrahedron Lett.*, 1999, **40**, 2199–2202 and references therein.

34 T. K. Chakraborty, S. Jayaprakash, P. Srinivasu, M. G. Chary, P. V. Diwan, R. Nagaraj, A. R. Sankar and A. C. Kunwar, *Tetrahedron Lett.*, 2000, **41**, 8167–8171.

35 R. M. van Well, H. S. Overkleeft, M. Overhand, E. V. Carstenen, G. A. van der Marel and J. H. van Boom, *Tetrahedron Lett.*, 2000, **41**, 9331–9335.

36 A. M. Costa and J. Vilarrasa, *Tetrahedron Lett.*, 2000, **41**, 3371–3375.

37 S. Hoppen, U. Emde, T. Friedrich, L. Grubert and U. Koert, *Angew. Chem., Int. Ed.*, 2000, **39**, 2099–2102.

38 A. Domling, M. Starnecker and I. Ugi, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2238–2239.

39 G. Mehta and S. S. Ramesh, *Chem. Commun.*, 2000, 2429–2430.