REVIEW

Recent Developments in Enediyne Chemistry

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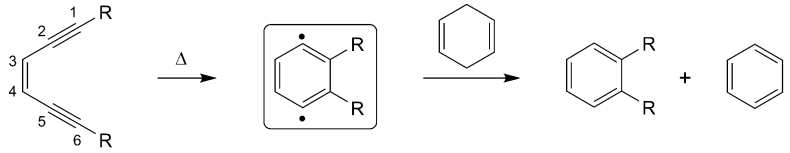
The enediynes are known for highly potent anticancer, antimicrobial, as well as cytotoxic activities. The discovery of enediynes from natural sources was achieved in late 1980s. They are presently of high interest, because they exert their biological action due to their ability to form a diradical, which abstracts H-atoms from the DNA backbone, thus causing cell death. Nowadays, the major works are dedicated to the syntheses of enediynes. This review covers recent developments in enediyne chemistry of the last few decades. It is subdivided in six chapters dealing with the discussion of the chemistry and biological significances of enediynes, and the factors responsible for a better activation of enediynes and potent biological evaluations.

Contents

1. Introduction. – Ever since the initial reports of the enediyne anticancer antibiotics in the late 1980s, researchers from a number of disciplines have been devoting increasing attention to their chemistry, biology, and its potential medical applications. Enediynes have their origin in various marine and terrestrial plant sources, and they are potent substantial class of antitumor, antimicrobial agents with high cytotoxic activities of established clinical efficacy. The commonly known potent antitumor and antimicrobial enediynes are calicheamicin [1], esperamicin [2], dynemicin [3], neocarzinostatin [4], kedarcidin [5], namenamicin [6], C-1027 chromophore [7], maduropeptin [8], N1999A2 [9], and shishijimicin [10], and recently found uncialamycin [11]. Due to their potent activity, fascinating mode of action, and novel molecular framework, enediynes immediatly attracted attention of chemists. So far, *ca.* 40 enediynes have been isolated from natural sources, and some of these compounds are by three order of magnitude more potent than other anticancer drugs.

The antitumor activity of these compounds is due to the presence of a highly unsaturated hex-3-ene-1,5-diyne unit that undergoes *Bergman* cyclization (BC) and generates a benzene-1,4-diradical, which abstracts H-atoms from the DNA backbone and causes cell death [12–15]. BC is a thermal rearrangement of (*Z*)-hex-3-ene-1,5-diynes to benzene-1,4-diyls, which, after quenching by H-atom donors, afford new benzene rings [16][17] (*Scheme 1*).

Scheme 1



To perform the BC in a controlled manner, different techniques have been explored, such as synthesis [18], photochemistry [19], and electrochemitry [20]. Recently, metal ions have been applied [21][22] to control the BC for a better efficacy. Also, in-depth studies are being conducted on factors, which affect the BC, such as electronic [23–28], geometric, and steric factors, and planarity, oxidation states, and transition states [29], *etc.*

Furthermore, recent studies revealed that even thermally stable enediynes exhibit biological activities [30–32], indicating that enediynes can have potential in the treatment of many infectious diseases, apart from their role in anticancer drug

discovery programs, such as antibacterial activity [23], protein degradation activity [33], and topoisomerase inhibitory activity [34]. These studies dealt with the requirements of lower cyclization temperature of enediynes to be biologically active [35]. Therefore, the aim is the syntheses of enediynes and the evaluation of their biological activities.

2. Natural Enediynes. – Natural enediynes were isolated from various marine and terrestrial plant sources. They are highly potent and represent clinically established classes of antitumor, antimicrobial, and cytotoxic agents. Calicheamicin (**1**) [1], esperamicins **2** and **3** [2], dynemicins **4** and **5** [3], neocarzinostatin chromophores **6** and **7** [4], lidamicins (C-1027) **8** and **9** [7], kedarcidin (**10**) [5], N1999-A2 (**11**) [9], maduropeptin (**12**) [8], namenamicin (**13**) [6], shishijimicins **14**–**16** [10], and recently found uncialamycin (**17**) [11] are the commonly known natural enediynes.

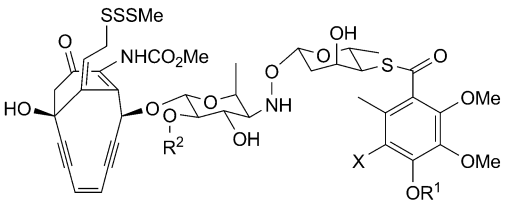
2.1. *Calicheamicin*. The cyclic ten-membered enediyne calicheamicins (**1**) were isolated from the soil bacterium *Micromonospora echinospora* spp. *calichensis* in 1986 (*Table 1*). The structure was proposed by *Lee et al.* [1] in 1987; later, configuration at one of the stereogenic centers was revised, and the synthesis was achieved by *Nicolaou* and *Dai* [23]. Calicheamicin exhibits high potency against murine tumors such as L1210, P338 leukemias, and solid neoplasms (colon 26 and B-16 melanoma), and was found extremely active against *Gram*-positive and *Gram*-negative bacteria. Its conjugation with rituximab enhanced its growth-inhibitory activity against BCL *in vitro* [23][36–38]. The conjugation to an antibody that recognizes CD33 (gemtuzumab ozogamicin) permits treatment of acute myeloid leukemia.

Table 1. *Calicheamicins*

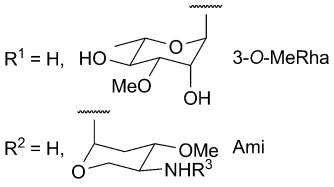
Calicheamicin	X	R^{1a})	R^{2a})	R^3
Calicheamicin β_1^{Br}	Br	3-*O*-MeRha	Ami	Me_2CH
Calicheamicin γ_1^{Br}	Br	3-*O*-MeRha	Ami	Et
Calicheamicin α_1^I	I	H	Ami	Et
Calicheamicin α_3^I	I	3-*O*-MeRha	H	–
Calicheamicin β_1^I	I	3-*O*-MeRha	Ami	Me_2CH
Calicheamicin γ_1^I	I	3-*O*-MeRha	Ami	Et
Calicheamicin δ_1^I	I	3-*O*-MeRha	Ami	Me

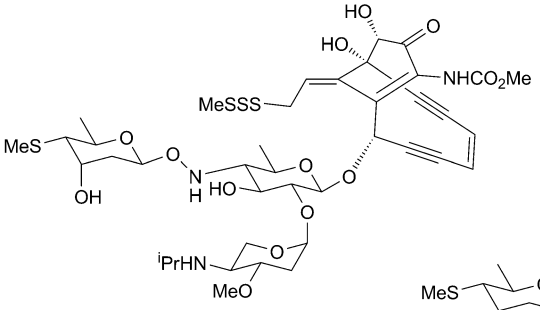
[a]) See *Formula* **1** for 3-*O*-MeRha and Ami.

2.2. *Esperamicin*. The cyclic ten-membered enediyne esperamicins (**2** and **3**) [2] were isolated from fermentation broth of *Actinomadura verrucosospora* in 1985 (*Table 2*) [39]. Esperamicins in conjugation with calicheamicins are the most powerful antitumor agents so far, which exhibit strong activities against a number of murine tumor models such as P388, B16, and M5076 [40] at injected doses of 0.1 μg/kg. Esperamicin A causes double-strand scission involving deoxyribose H-atom abstraction from the 1′- and 5′-position, while esperamicin leads to H-atom abstraction from the 4′- and 5′-position.

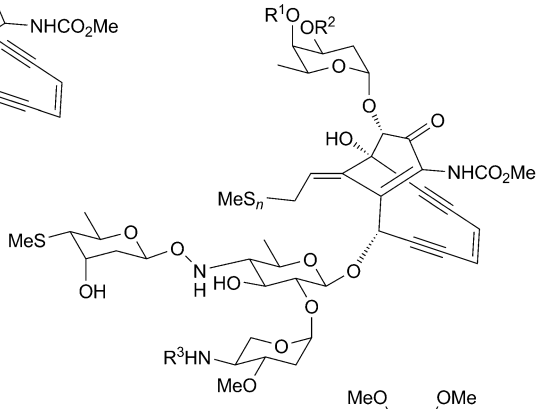


Calicheamicin (**1**)



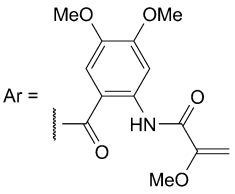


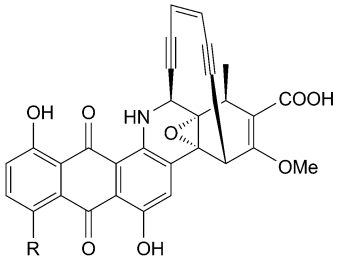
Esperamicin C (**3**)



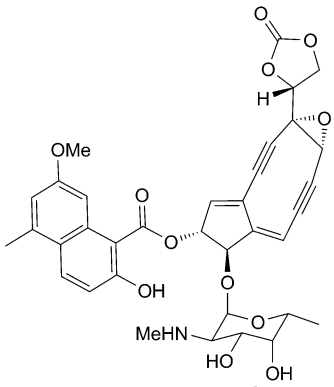
Esperamicin (**2**)

n = 3, 4
R^1 = H, Ar
R^2 = Ar, H
R^3 = ^{i}Pr, Me, Et

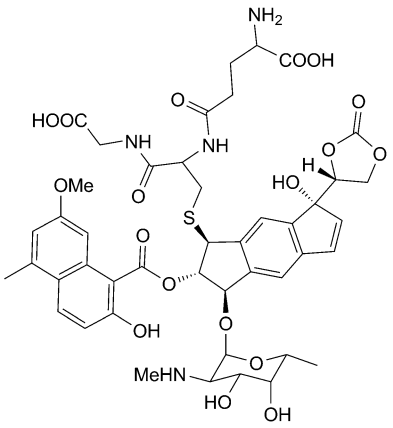




Dynemicin A (**4**) R = OH
Deoxydynemicin A (**5**) R = H



Neocarzinostatin (**6**)



Post-activated neocarzinostatin (**7**)

Table 2. *Esperamicins*[a])

Esperamicin	*n*	R^1	R^2	R^3
Esperamicin A_1	3	H	Ar	^{i}Pr
Esperamicin A_{1b}	3	Ar	H	^{i}Pr
Esperamicin A_{1c}	3	H	Ar	Me
Esperamicin P	4	H	Ar	^{i}Pr
Esperamicin A_2	3	H	Ar	^{i}Pr
Esperamicin A_{2b}	3	Ar	H	Et
Esperamicin A_{2c}	3	Ar	H	Me

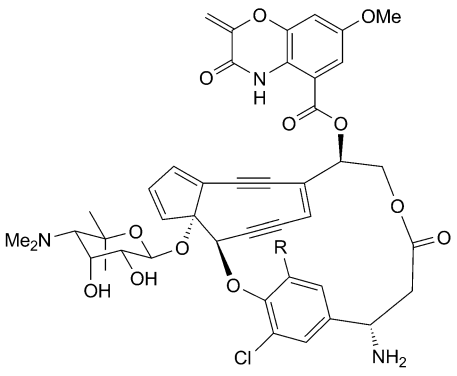
[a]) See *Formula* **2** for substituents.

2.3. *Dynemicin*. The cyclic ten-membered enediyne dynemicin (**4**) [3] was isolated from the fermentation broth of *Micromonospora chersina* [23]. The structure was first reported in 1990 by *Konishi et al.* [3]. Dynemicin A (**4**) exhibits high potency against a variety of cancer cell lines such as P388 leukemia and B16 melanoma [3][23], and shows promising *in vivo* antibacterial activity with slightly lower toxicity. Subsequently, a second member of this family, bioactive deoxydynemicin A (**5**) was isolated from *Micromonospora globosa* MG331-hF6 [41] with a similar activity as **4**. Dynamicin A (**4**) cleaves DNA duplex causing both single- and double-stranded cuts.

2.4. *Neocarzinostatin*. The cyclic nine-membered enediyne neocarzinostatin (**6**; NCS) and its post-activated product **7** [4] represent the prototypical chromoprotein antitumor antibiotic, consisting of 1 : 1 mixture of an (NCS) apoprotein [42] and a NCS chromophoric [43] molecule, and were isolated from *Streptomyces carzinostaticus* var. F-41 (ATCC15944) in 1965. Recent studies, however, indicated that the apoprotein may also contribute actively to the cytotoxicity through selective proteolytic activity [44] against histones *in vitro*. It intercalates into DNA *via* its naphthoate group and remaining part of molecule in the minor groove [40][45]. It has been demonstrated that at least 80% of the DNA cleavage by NCS chromophore **6** leads to the aldehyde of the DNA backbone [46]. The SMA (polystyrene-co-maleic acid)–NCS conjugate has been used in the treatment of hepatoma in Japan since 1994, and (SMA-NCS)-lipoidal conjugate to treat tumors in the lung, stomach, pancreas, gall bladder, as well as lymphoma and melanoma.

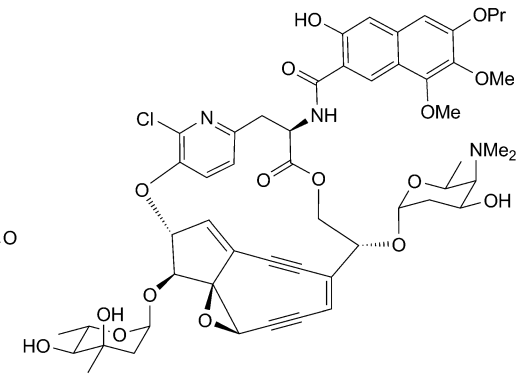
2.5. *C-1027 Chromophores*. The cyclic nine-membered enediyne C-1027 chromophores **8** and **9** [7] were isolated from culture filtrates of *Streptomyces globisporus* in 1988, and the exhibit potent antitumor activities against leukemia L1210, P388, and ascites hepatoma H22 cells [32][47–49]. They also show highly potent cytotoxic activity to myeloma cells and inhibit tumor growth in mice. Their remarkable inhibition on the growth of colon cancer, human liver cancer, and epithelial tumor cells was also reported [50].

2.6. *Kedarcidin*. The structure of the cyclic nine-membered kedarcidin (**10**) [5], an antitumor enediyne, first reported in 1991 as fermentation product of *Actinomycete* strain (L585–6), has been now revised [51]. It shows potent *in vivo* antitumor activity against implanted P388 leukemia (3.3 μg/kg) and B16 melanoma cells (2 μg/kg), and exhibits potent activity against *Gram*-positive bacteria [5][44]. It strongly inhibits the

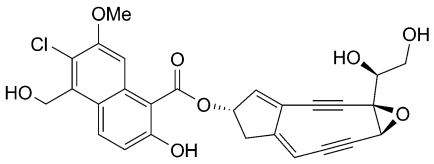


C-1027 Chromophores

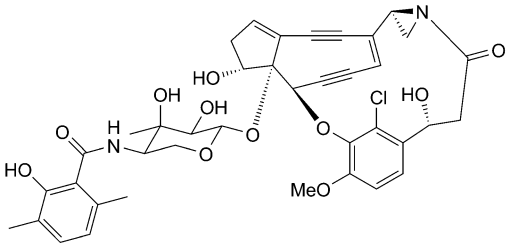
8 R = H
9 R = OH



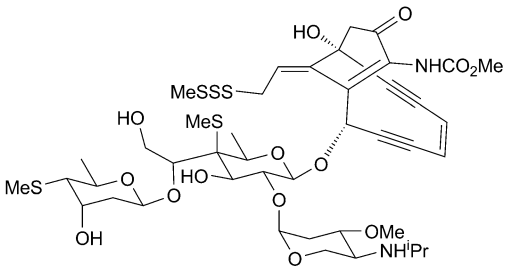
Kedarcidin (**10**)



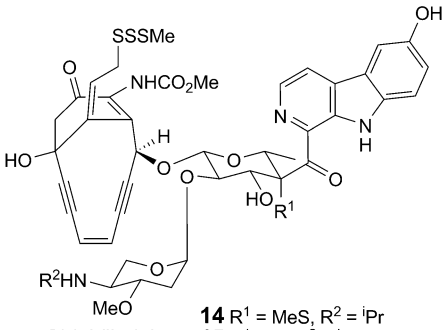
N1999A2 (**11**)



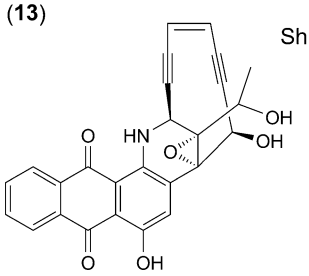
Maduropeptin (**12**)



Namenamicin (**13**)



Shishijimicins **14** R^1 = MeS, R^2 = ^{i}Pr
15 R^1 = H, R^2 = ^{i}Pr
16 R^1 = MeS, R^2 = Et



Uncialamycin (**17**)

growth of various tumor cell lines and bacteria, and cleaves DNA in a base-specific manner [6][52].

2.7. *N1999-A2* (NA2). The new antitumor and antibiotic cyclic nonprotein nine-membered N1999-A2 enediyne (**11**; NA2) was isolated from the broth filtrate of *Streptomyces* sp. AJ9493 [9]. It strongly inhibits the growth of various tumor cell lines and bacteria, and cleaves DNA in a base-specific manner [7].

2.8. *Maduropeptin*. The cyclic nine-membered antitumor and antibiotic enediyne maduropeptin (**12**) was isolated from the broth filtrate of *Actinomadura madurae* in 1991 [8]. It consists of a 1:1 complex of labile nine-membered enediyne and an acid-stabilizing protein (H_2O-soluble carrier protein 32kDa). It exhibited potent inhibitory activity against *Gram*-positive bacteria and strong *in vivo* antitumor activity against P388 leukemia and B16 melanoma implanted mice [53]. Total synthesis of maduropeptin has been achieved recently [50].

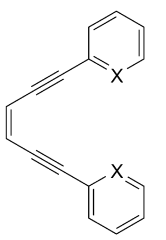
2.9. *Namenamicin*. The cyclic nine-membered enediyne namenamicin (**13**) has been isolated from marine orange ascidian *Polysyncraton lithostrotum* in very low yield [6] (1 mg from 1 kg of frozen tissues). It exhibited potent *in vivo* antitumor activity against P388 leukemia (mice) and showed also potent antimicrobial activity.

2.10. *Shishijimicin*. The cyclic nine-membered shishijimicins A–C (**14**–**16**, resp.) have been isolated from Japanese marine invertebrate ascidian *Didemnum proliferum* (collected in southern Japan). They show potent cytotoxicities against 3Y1, HeLa, and P388 cell lines [10]. They exhibit unique activities in the 3Y1 cell morphology assay [54].

2.11. *Uncialamycin*. Recently, the cyclic ten-membered enediyne uncialamycin (**17**) was isolated from the surface of lichen *Cladonia uncialis*, collected in British Columbia [11]. It exhibits potent *in vitro* antibacterial activity against *Gram*-positive and *Gram*-negative bacteria such as the human pathogens *Staphylococcus aureus* (*MIC* 0.0000064 μg/ml), *Escherichia coli* (*MIC* 0.002 μg/ml), and *Burkholderia cepacia* (*MIC* 0.001 μg/ml). The synthesis of this compound has been achieved recently [55].

3. Acyclic Enediynes. – Due to highly potent antitumor, antimicrobial, and cytotoxic activities of natural enediynes, the synthesis of enediynes using different approaches and methodologies has been in the focus of scientists. Recently, *Lin et al.* [56] have reported the syntheses of thermally stable and biologically active enediynes **18**–**21**. Among these, enediynes with aromatic N-heterocycles at their alkyne side, **18** and **19**, showed growth inhibition effects on a full panel of 60 human cancer cell lines, with most of the average IC_{50} values ranging from <0.01 to 96.9 μM. Some of the amine-based enediynes **20** exhibited the highest cytotoxic activities against the cancer cell lines at the 10^{-7} M concentration range. During the cell-cycle analysis, a moderate-to-high apoptotic progress induction was shown by some amine and N-containing enediynes **18**–**21**. A series of compounds of type **22** also exhibited growth inhibition activities, especially against the human leukemia RPMI-8226 (0.4 μM) and SR (0.02 μM) cell lines [57]. Some compounds also induced significant apoptotic progress in the cell-cycle assay with the K-562 cell line, while the novel enediyne THDA (**23**) act as antineoplastic agent against human leukemia K562 cells [58]. THDA-Induced apoptosis was associated with the upregulation of Bax and downregulation of X-linked inhibitor of apoptosis (XIAP), as well as the activation of caspase-3 and caspase-9.

In addition, the mitogen-activated protein family of kinases, including c-Jun N-terminal kinase (JNK) and extracellular signal-regulated protein kinase (ERK), and



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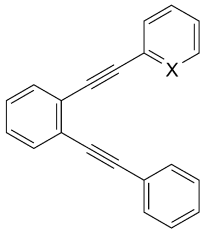
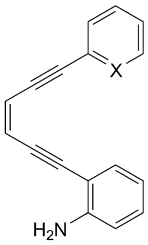


19 X = CH, N



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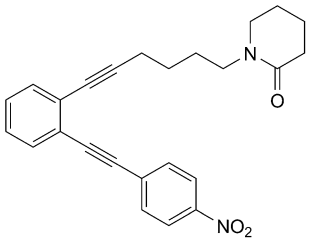

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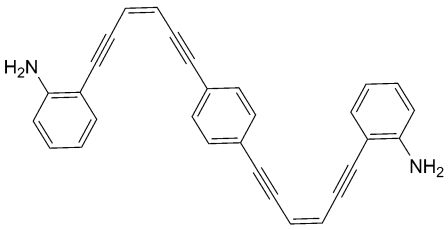

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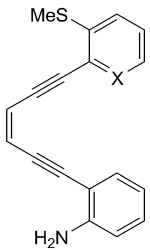

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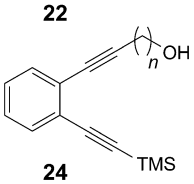

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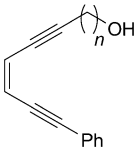
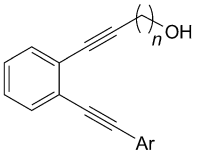
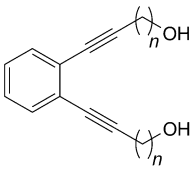


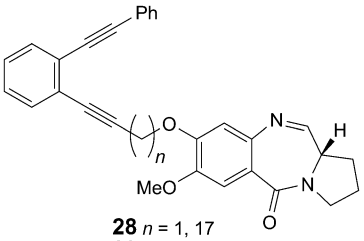
26 *n* = 1, 2



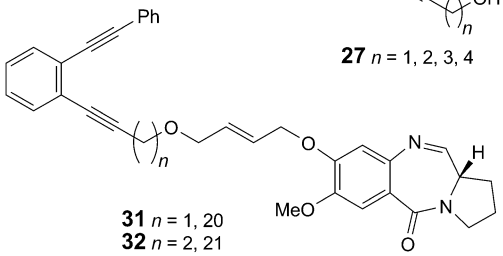
25 *n* = 1, 2, 4; Ar = 2-MeO–C_6H_4, pyridin-2-yl, thiophen-2-yl, 2-MeS–C_6H_4, 2-CF_3–C_6H_4, 3-MeS–C_6H_4, 3-HO–C_6H_4, 3-CF_3–C_6H_4, 4-HO–C_6H_4, 4-CF_3–C_6H_4, 4-NC–C_6H_4



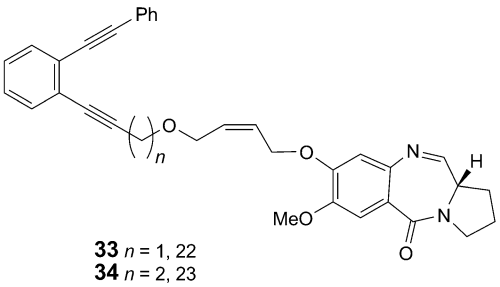
27 *n* = 1, 2, 3, 4



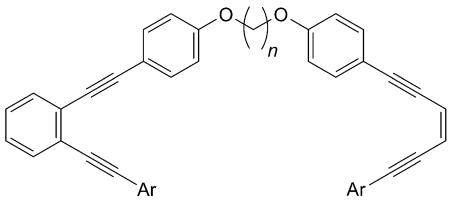
28 *n* = 1, 17
29 *n* = 3, 18
30 *n* = 4, 19



31 *n* = 1, 20
32 *n* = 2, 21



33 *n* = 1, 22
34 *n* = 2, 23



n = 5 **35** Ar = 2-$H_2NC_6H_4$
n = 6 **36** Ar = 2-NC–C_6H_4
37 Ar = 2-$H_2NC_6H_4$
38 Ar = 2-NO_2–C_6H_4
39 Ar = 2-$MeOC_6H_4$
40 Ar = 2-F_3C–C_6H_4
41 Ar = pyridin-2-yl

the transcription factor c-Jun were all activated by phosphorylation after 6-h exposure to THDA (**23**). On the basis of these findings, it was suggested that the activation of JNK and ERK is involved in the **23**-induced apoptosis of K562 cells.

Lo et al. [59] disclosed that enediynes with the terminal OH group **27** exhibit potent anticancer activities. Enediyne **25** with a 4-(trifluoromethyl)phenyl group as Ar showed the most potent growth-inhibition activity against all tumor cell lines at low concentration, such as, SR (0.4 μM) and MDA-MB-435 (0.8 μM), and almost completely blocked cell cycle in G2/M phase *via* controlling cyclin A and Cdc25C expression. The growth-inhibition activities of these novel enediynes **25**–**27** were tested in the NCIs (National Cancer Institute) *in vitro* anticancer screen with the panel of 60 human tumor cell lines [60]. Compounds **26** and **27** were not able to pass NCI anticancer assay; however, **25** displayed a broad-spectrum of inhibition on various cancer cell lines.

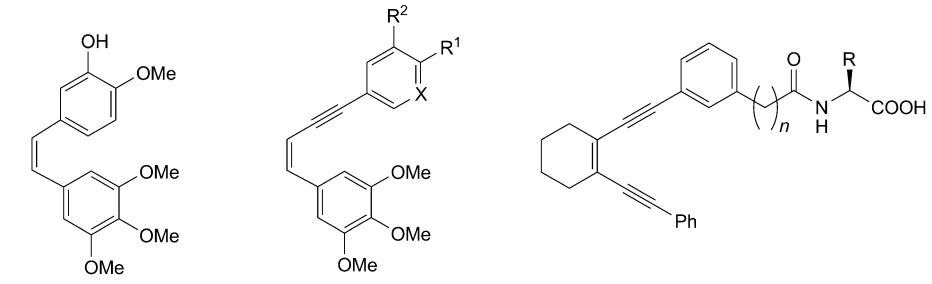
Hua et al. [61] recently reported a series of ether-bridged novel enediynes which are the conjugates of 1,2,3,11a-tetrahydrobenzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one [62] linked with the enediynes **28**–**34**. In conjugation, most of the hybrids exhibited higher cytotoxicities against human cancer cell lines. At the same time, a series of new acyclic symmetric bis-enediynes **35**–**41** has been synthesized [63], which exhibit growth inhibition on several human tumor cancer cells. Among them, **41** showed strong inhibition activity against the human leukemia CCRF-CEM (GI_{50} 0.04 μM) and HL-60 (GI_{50} 0.09 μM) cell lines. The cell-cycle analysis showed that compound **41** arrests cell cycle *via* inhibiting cyclin A and cyclin B expressions in low concentration and induces a significant apoptosis progress at high concentration.

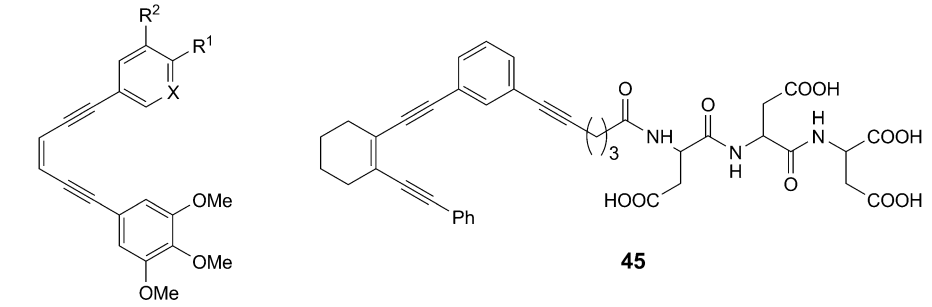
Inspired by the biological importance of combretastatin A-4 [64], *Provot et al.* [65] developed a method for the preparation of enynes **42** and enediynes **43**, analogs of combretastatin. Some derivatives of enyne **42** and enediyne **43** inhibited tubulin polymerization with IC_{50} values in the range of 60–70 μM, while other compounds did not show any significant activity. At a concentration of 10^{-5} M, some of these compounds exhibited a marginal activity towards KB, MCF7, and MCF7R cells. Some enediynes, **44** and **45**, were successfully employed for the selective degradation of target proteins [66].

Enediyne **46** undergoes photochemical cyclization to provide isomeric indenes **47** and **48** (*Scheme 2*) [67]. The cyclization process was found to be different from the BC. The presence of strongly electron-withdrawing tetrafluoropyridin-4-yl (TFP) substituents renders the photo-induced electron transfer from cyclohexa-1,4-diene (CHD) to the singlet state of the enediynes highly exothermic. These compounds have been used for the development of enediyne based DNA photocleaving agents.

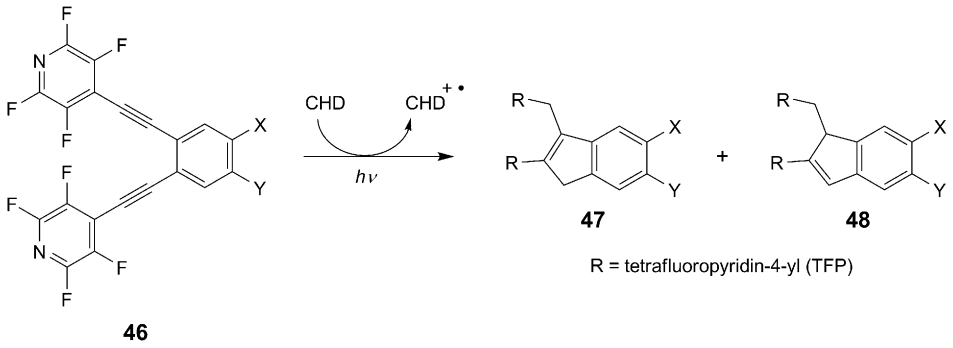
The syntheses of lysine-enediyne conjugates **49** and **50** were also accomplished [67], and it has been shown that enediyne–amino acid conjugates cause double-strand cleavages in DNA. According to the literature, polyamine transporters mediate the uptake of extracellular polyamines into the cell, and this transporter is up-regulated in tumor cells, which requires large amounts of polyamines. Amine–enediyne conjugates **51**–**54** have also been synthesized, and these compounds exhibited biological activities due to DNA cleavage *via* BC.

Recently, *Jeric et al.* [68] reported the first example of a enediyne-linked dipeptide **55**. BC of these compounds was studied using CHD as the H-atom donor. On the other hand, *Basak et al.* [69] synthesized the enediyne–tripeptide conjugates **56**–**60** without

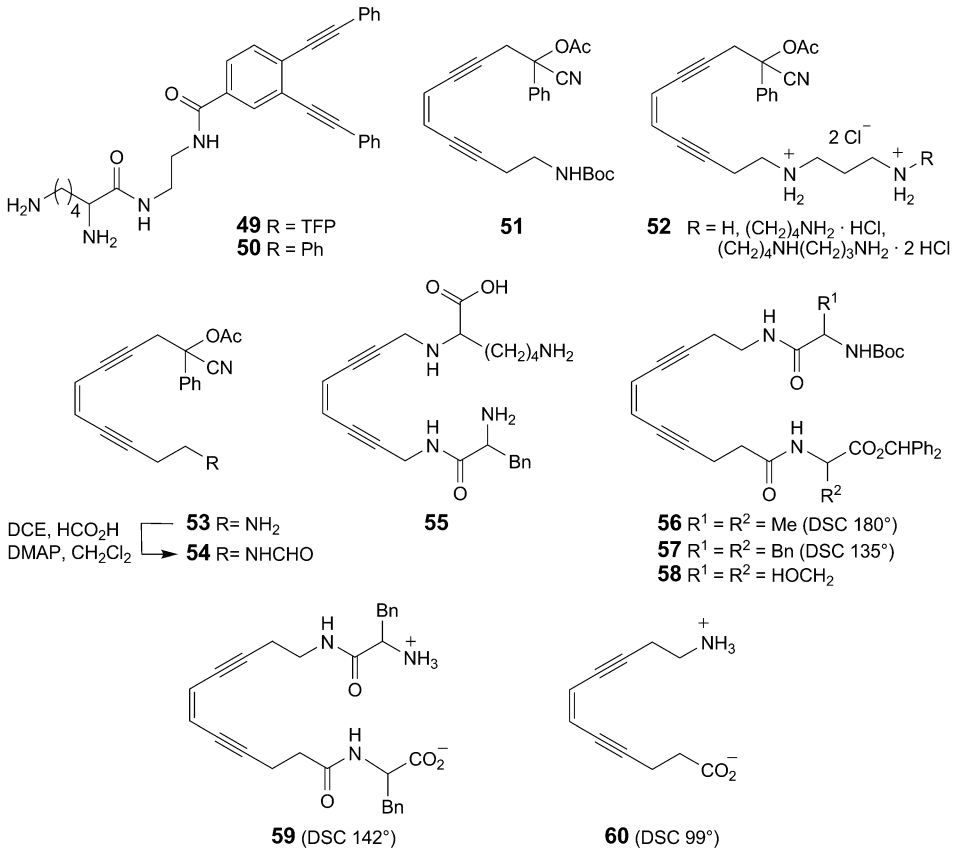




Scheme 2



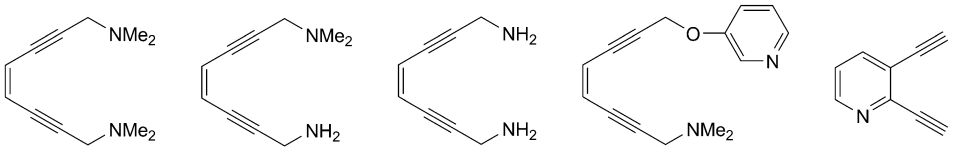
any racemization by *Sonogashira* coupling and studied their thermal behavior. The thermal reactivity of these conjugates was shown to be dependent on the nature of the side chain in the amino acids. In case of peptide **57**, the onset temperature for BC was 135°, whereas compound **56** underwent BC at 180°. Thus, BC was more facile for



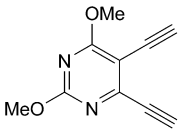
peptide **57** than for **56**, and this indicates that the acetylenic arms in peptide **57** are closer. Compound **58** was not found very informative, because there was no sharp rise in the DSC (differential scanning calorimetry) curve. Peptide **59**, obtained by deprotection of **57** with CF_3COOH (TFA), showed an onset temperature for BC starting at 130°. The enediyndiyl-bridged amino acid **60** showed the BC onset temperature 99°, which was quite low with respect to the other peptides. In all the peptides, the β-N–H showed a slightly weaker intramolecular H-bonding compared with the α-N–H. The analysis of the CD spectra of these peptides, as well as the variation of chemical shifts with temperature, revealed the presence of a β-sheet-nucleating conformation in equilibrium, with a conformation induced by H-bond formation between the C=O and NH belonging to the enediynyl amino acid. Thus, it is assumed that the cyclization temperature of enediynes unit and steric bulk at the ene or yne position will affect the BC.

On the basis of steric-bulk studies, *Rawat* and *Zaleski* [70] synthesized some acyclic enediynes **61**–**64** *via Sonogashira* coupling. The cyclization temperatures of these compounds were determined on neat materials by DSC, and a remarkable variation of 80° across the series was observed. The origin of the gradient is derived from the steric encumbrance imposed upon the alkyne termini by the N-containing substituents at the

1,8-positions of the enediyne framework. The low onset temperature for reactivity of the acyclic enediyne **63** indicates that **63** may be an extremely important ligand for generating thermally reactive and therapeutically useful metallo-enediyne complexes. This series of enediynes also highlights the importance of ligand design in influencing BC temperatures and points toward the use of sterically unproblematic ligands to achieve lower metallo-enediyne cyclization temperatures.



61 (DSC 186°) **62** (DSC 139°) **63** (DSC 106°) **64** (DSC 149°) **65**



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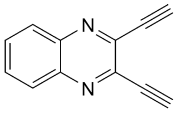

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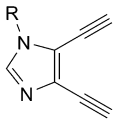


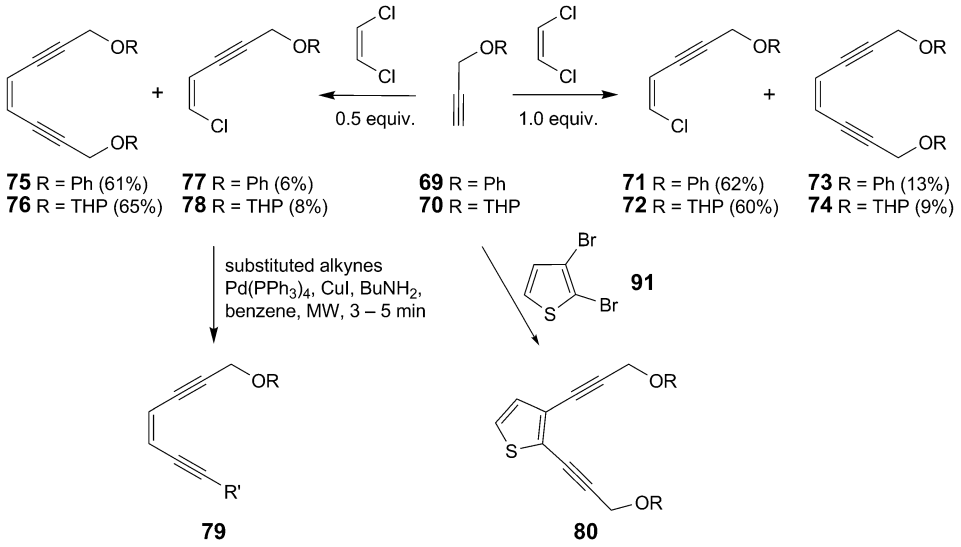
68 R = Me, ^{t}Bu, Ph, substituted phenyls

Russell and co-workers [71] have observed that electron-deficient heteroarene-diynes **65** and **66** seem to have lower activation energies for BC product formation than the quinoxaline derivative **67** or 1,2-diethynylbenzene. The BC temperature for imidazole derivatives **68** depends on the nature of the R substituent [72]. These compounds present considerable potentials for the development of molecules of pharmaceutical use.

By taking advantage of visible-light molecular photoswitch, *Sud et al.* [73] synthesized some thiophene-containing enediynes (at ene position) for BC. Low-molecular-weight organic gelator-based, and amide-functionalized (phenylethynyl)-thiophenes [74] were synthesized which were capable of immobilizing a variety of organic solvents to form stable organogels. Self-assembly of these molecules *via* cooperative H-bonding and π-stacking induced gelation of a variety of organic solvents. These molecules show strong π–π^* absorption in the UV and near UV-region in dilute solution. The fluorescence maxima exhibit a bathochromic shift to 506 and 523 nm in gelling solution and film, respectively. The morphology of dried gels of these molecules was studied by scanning electron microscopy (SEM) and transmission electron microscopy (TEM). SEM and TEM studies revealed the formation of fiber-like nanostructures. Higher conjugated enediynes do not exhibit antitumor activity, and they are not capable to perform BC. Tetrakis(phenylethynyl)ethene was the first TEE (=tetraethynylethene=3,4-diethynylhex-3-ene-1,5-diyne) derivative [75]. These compounds are kinetically very stable and display high melting or decomposition points, which, in the case of arylated derivatives, reaches 200° and higher.

A series of enediynes was synthesized for the first time by using microwave irradiation (MW) for *Sonogashira* couplings (*i.e.*, **71**–**80**; *Scheme 3*) [76]. These compounds were characterized successfully, and their yields were almost the same as those obtained by conventional methods. However, the microwave procedure afforded

Scheme 3

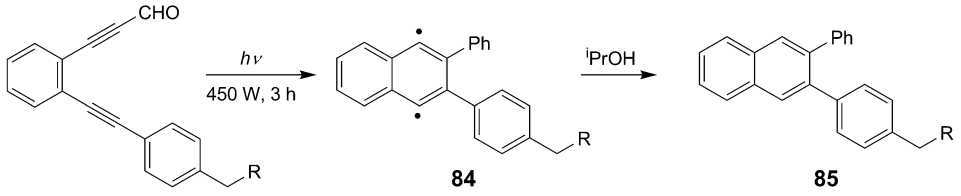


the enediynes within 3–5 min, whereas the conventional methods required reaction times of 12–14 h.

Sahu et al. [77] reported on mechanistic investigations of the rearrangement of 2,3-unsaturated 1,4-bis(alkylidene)carbenes for the synthesis of enediynes. The method involves the dibromomethylenation of dialdehydes under *Corey–Fuchs* conditions (CBr_4, Ph_3P, and Zn) and treatment of the resulting tetrabromo derivatives with BuLi or lithium diisopropylamide (LDA) to afford enediynes. The other method involves a base-mediated reaction of enedialdehydes with diethyl 1-diazo-2-oxopropylphosphonate (*Bestmann–Ohira* reagent) and subsequent transformation of the bis-diazo compounds, generated *in situ*, to enediynes. For the syntheses of various heteroatom-based (S, Se, and P) enediynes, quenching of the acetylides with suitable electrophiles by using deuterium-labeling experiments has been applied.

Recently, *Falcone et al.* [78] synthesized a series of functionalized simple aryl enediynes **81**–**83** (*Scheme 4*). The building blocks were used to effect conjugation to carrier polyethylene glycol (PEG) templates **82**, which allowed subsequent coupling to

Scheme 4

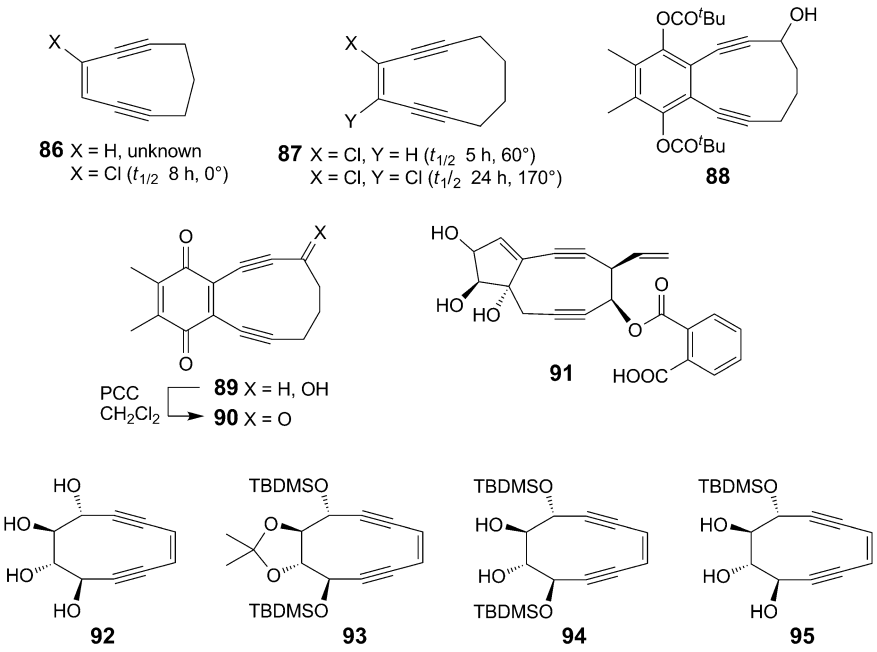


81 R = $OCO(CH_2)_2(OCH_2CH_2)_{12}O(CH_2)_2COOH$
82 R = $OCO(CH_2)_2(OCH_2CH_2)_nO(CH_2)_3NH_2$
83 R = S-Au

a cardiac-targeted monoclonal antibody, and the bioconjugates underwent successful photo-BC. For a step towards enediyne nanoparticles, the authors synthesized a surface modified (Au) nanoparticle conjugate **83**, the size of which was confirmed by transmission electron microscopy (TEM) analysis. It was anticipated that **83** acts as long-circulating photo-active prodrug.

4. Cyclic Enediynes. – Nowadays, most of the work on enediyne chemistry is focused on the thermal reactivity modulation and anticancer activity evaluation; however, very little is known about the biological importance of thermally stable cyclic enediynes. To study the biological significance of thermally stable enediynes, the syntheses of cyclic 9-, 10-, 11-, 12-, 13-, 14 (or higher)-membered enediynes have been attempted.

4.1. *Nine- and Ten-Membered Enediynes. Jones et al.* [28] measured the $t_{1/2}$ value of the nine-membered Cl-substituted enediyne **86**. The parent enediyne **86** is still unknown. This study demonstrated that substitution of one olefinic H-atom by Cl enhanced the cyclization temperature of the resulting enediynes **86** and **87**. In general, the evidence of the influence of the C=C character on BC is not very clear (*i.e.*, **88** and **90**). *Nicolaou* and *Dai* [23] have shown that quinone enediyne undergo BC at a much faster rate than its hydroquinone counterpart. The stable cyclic enediyne **88** exhibited no DNA-cleaving activity at pH 7.4 and 37°, whereas compounds **89** and **90** showed significant DNA-damaging properties due to formation of the cyclized products *via* the corresponding diradicals. These compounds exhibited changing degrees of antitumor activity against a variety of cell lines with the most impressive results obtained with compounds **89** and **90**.

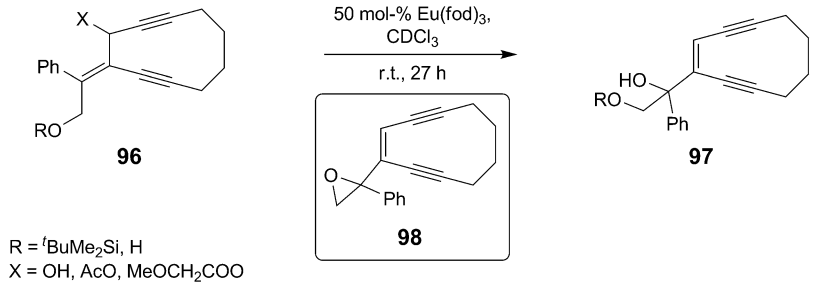


Nine-membered enediynes have received considerable attention for many years due to their potent DNA-cleaving activity. Thus, *Tanaka et al.* [79] reported the synthesis of the masked nine-membered enediyne **91**, recently.

Cyclic ten-membered tetrahydroxy enediynes **92**–**95** was reported by *Konig* and co-workers [80]. They were enantiomerically pure. The OH groups render the compounds H_2O soluble, and at the same time they lock the ring conformation and control the enediyne reactivity. The thermal reactivity of enediynes **92**–**94** was investigated by thermolysis and monitored by HPLC analysis [81]. The cyclization of **94** (TBDMS = (*t*-Bu)Me_2Si) was performed in benzene/cyclohexa-1,4-diene (CHD) at 69°, and the formation of the expected BC product was confirmed by HPLC/MS. Tetrahydroxy enediyne **94** is H_2O-soluble, therefore, the thermal cyclization of this compound was investigated in aqueous solution. The thermolysis data confirmed that removal of the isopropylidene group in **93** transforms the stabilized enediynes into thermally reactive compounds. To investigate the concept of enediyne stabilization and activation *in vitro*, the cytotoxicities of compounds **92**–**94** were tested against human breast cancer cells MDA-MB-231 in the crystal violet assay. Compound **93**, stabilized by the isopropylidene protecting group, had no effect on cell growth, whereas, for **92** and **94**, a weak growth inhibition was observed. However, in comparison to cisplatin, a clinically used anticancer agent, the inhibitory concentrations of enediynes **92** and **94** were very high.

A series of substituted enediyne prodrugs **96** has been synthesized by *Dai* and co-workers [82][83] under *Sonogashira* and intramolecular *Nozaki–Hiyama-Kishi* key conditions (*Scheme 5*). The synthesized enediynes **96** and **97** exhibited potent anticancer activities. However, the expected epoxy enediyne **98** was not obtained. These results imply that either the epoxide ring is relatively difficult to form due to ring strain or epoxy enediyne **98** cannot survive in the presence of the *Lewis* acid $Eu(fod)_3$. These enediyne compounds showed cytotoxicities at *ca.* 1 μM against the P388 cancer cell line. On the basis of the IC_{50} data, a structure–activity relationship was discussed in terms of the allylic rearrangement mechanism *via* an allylic cation intermediate. Recently, substituted enediyne analogs of compound **96** and **97** have been reported. These compounds have been evaluated for DNA cleavage activity at pH 8.5 buffer without UV irradiation. The enediyne prodrugs **96** and **97** (*Scheme 5*) exhibited concentration- and time-dependent DNA strand scission in basic buffer (pH 8.5) at 37°. These results indicated that a base-promoted intramolecular allylic rearrangement takes place to convert **96** and **97** into a reactive epoxy enediyne **98**, which can cause

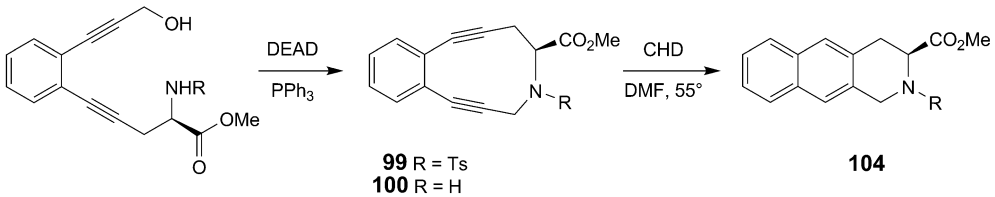
Scheme 5



DNA strand cleavage most likely *via* H-atom abstraction from the sugar-phosphate backbone. With mass spectrometry, the epoxy enediyne was detected in the incubation mixture of the acetate **96** under the conditions used for DNA-cleavage experiments. Based on these results, some of enediyne prodrugs were identified to be potentially useful for photoactive prodrugs.

Du et al. [84] synthesized ten-membered enediynes with versatile functional groups, **99**–**103** (*Scheme 6*; DEAD = diethyl azodicarboxylate), which undergo BC to afford the 1,4-diradicals that help to cleave the double-stranded DNA. These compounds undergo BC at 55°. The *N*-tosyl substituted derivative **99** was shown to nick double-stranded supercoiled DNA. *N*-Arylsulfonyl substitution on the ring promoted the cyclization, compared to *N*-mesyl or acyl substitution. It is possibly due to a π–π stacking effect as well as an *endo*-relationship of the aryl group with the diyne part that is present in both the solid state and in solution. In addition, **99** cleaved double-stranded DNA upon heating in a dose dependent manner.

Scheme 6

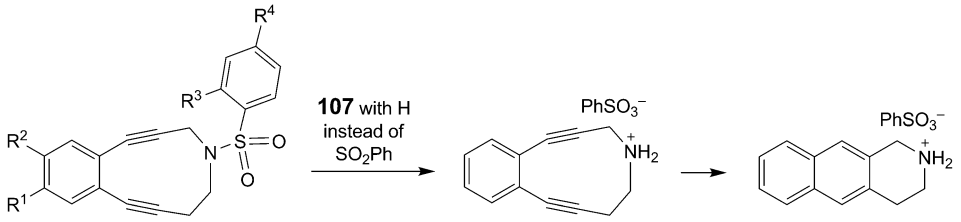


99 R = Ts
100 R = H
101 R = Ac
102 R = 4-(MeO)$C_6H_4SO_2$
103 R = 3,4-$(MeO)_2C_6H_3SO_2$

104

Recently, *N*-substituted ten-membered enediynes were also synthesized *via* an intramolecular *Mitsunobu* reaction by *Basak* and *Kar* [85] to study the electron-withdrawing effect of the substituents on the reactivity. The authors found that the electron-withdrawing effect of the NO_2 group in **105**, **106**, and **108** (*Scheme 7*), or the positive charge on the free ammonium salt **109** are responsible for decrease of the cyclization temperature in comparison with **107**. These amino enediynes are converted

Scheme 7



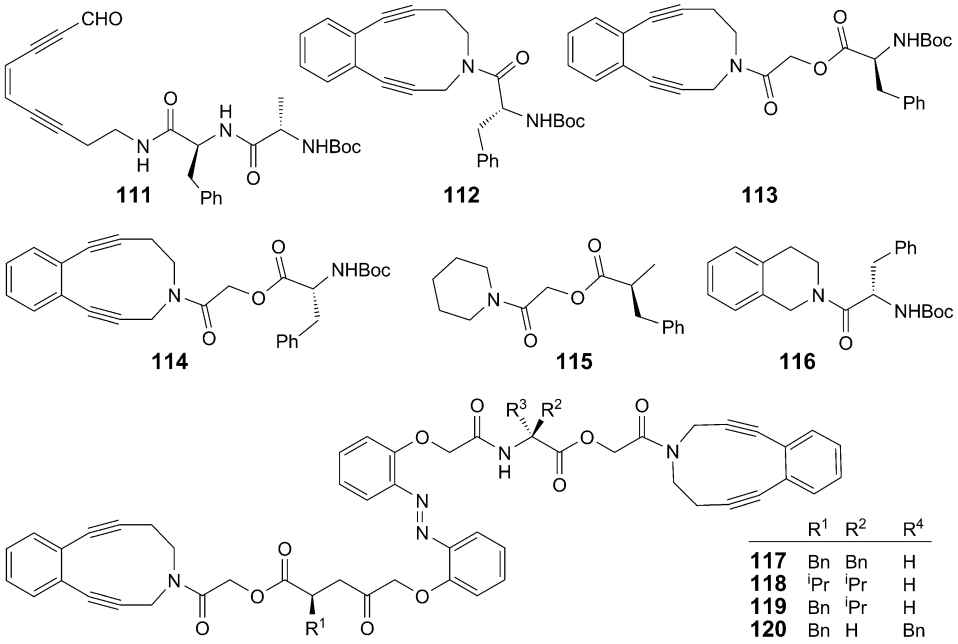
105 $R^1 = NO_2$, $R^2 = R^3 = R^4 = H$ (BC 166°)
106 $R^1 = H$, $R^2 = NO_2$, $R^3 = R^4 = H$ (BC 128°)
107 $R^1 = R^2 = R^3 = R^4 = H$ (BC 240°)
108 $R^1 = R^2 = R^3 = H$, $R^4 = NO_2$ (BC 110°)

109

110

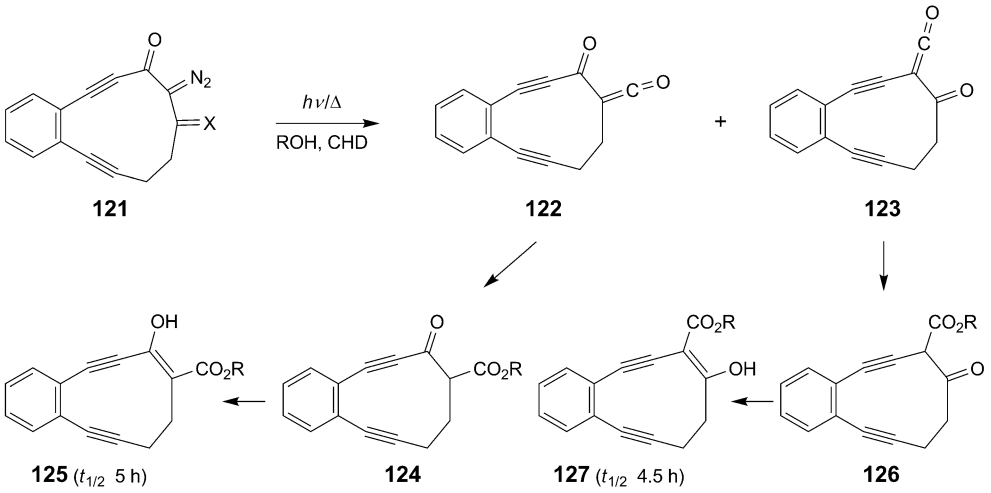
to cyclic ammonium salts which lower the activation barrier for BC to such an extent that the molecule can impose damage to double-stranded DNA.

Basak and co-workers also synthesized novel enediyne–amino acid conjugates **111**–**114** [86], which are potent inhibitors of α-chymotrypsin activity. The phenylalanine moiety in the synthesized molecules enhanced the specificity of these molecules. The role of enediynes in inhibiting the enzyme is clearly established by compounds **115** and **116** which are poor inhibitors. The exact role of the enediynes in the inhibition of enzyme is not yet well understood, but, possibly, protein cleavage *via* diradical formation takes place. The authors are trying to form more reactive enediynes to inhibit the protease connected with pathogenesis of various diseases like AIDS. Simultaneously, *Basak et al.* synthesized enediyne–amino acid C_2-symmetric hybrids, **117**–**120**, by using an amino acid linker [87]. DNA-Binding and -cleavage studies have established a higher reactivity of the (*Z*)-isomers. This work opened up the possibility of enhancing the DNA-cleaving efficiency of the C_2-symmetric enediynes *via* photochemical (*E*)/(*Z*) isomerization. *Ray* and *Basak* synthesized peptide–enediyne hybrides, which undergo selective intramolecular peptide-chain cleavage by the 1,4-diyl radical formed, the potential intermediate of the enediyne system [88].



Karpov and *Popik et al.* [89] used the eleven-membered enediyne **121** to synthesize ten-membered cyclic enediynes **122** and **123** (*Scheme 8*), which, upon irradiation or thermolysis, underwent *Wolff* rearrangement [90] to give reactive ten-membered enediynes **124** and **125** from enediyne **122**, and enediynes **126** and **127** from enediyne **123**. Compound **125** underwent spontaneous BC. Low-temperature photolysis of **121** allowed isolation of the unstable keto ester **124**, which underwent BC with $t_{1/2}$ 5 h at 36°

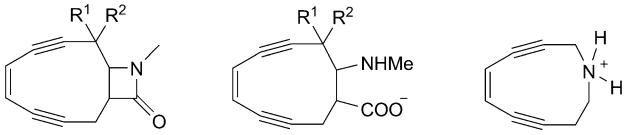
Scheme 8



in ^{i}PrOH. However, enediyne **125** was not detected in the photolysis even at 0°. This observation allowed the conclusion that enediyne **125** was also formed in the photo-*Wolff* reaction of **124** but underwent rapid thermal BC. An initial evaluation of the DNA cleavage ability of photogenerated ten-membered ring enediynes **124** and **125** was carried out by using supercoiled plasmid DNA cleavage assays. Thus, determined ratio **125**/**127** was 54:31, in the presence of a small amount (10%) of the diketone derived from **121** with =O instead of $=N_2$.

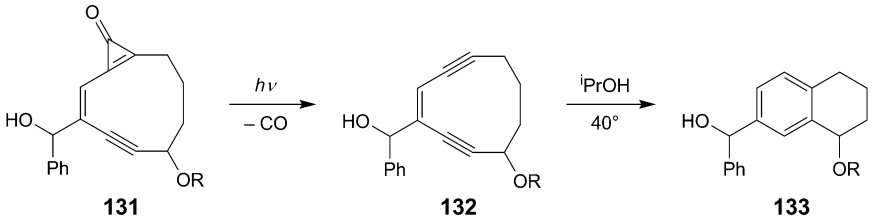
Banfi et al. [91–93] synthesized various substituted *trans*-fused ten-membered cyclic enediyne β-lactams. In the case of R^1 and R^2 are H and OH, respectively, the enediynes **128** and **129** are remarkably stable both in solution and in the solid state, and could be smoothly transformed to the corresponding acetyl and methyl derivatives. Heating **128** at 100° for several hours in the presence of CHD gave no reaction. However, when **128** with R^1 = MeO and R^2 = H was treated with 1N HCl in MeOH in presence of CHD for 2 h, complete transformation to the benzene product was observed. Recently, fused enediyne β-lactams were synthesized by intramolecular *Kinugasa* reaction [94]. DSC Studies indicated a significant influence of the β-lactam ring upon the reactivity of these enediynes. It was also reported that compound **130** led to cleavage of both single and double strands of plasmid DNA at μM concentrations.

The cyclopropenone-containing enediyne **131** was synthesized in ten steps by *Poloukhtine* and *Popik* [95]. The crucial cyclization step was accomplished under



Nozaki conditions [53][96][97], while the endocyclic C=C bond has been introduced by allylic rearrangement. Compound **131**, in which one C≡C bond is replaced by a cyclopropenone functionality, was designed for UV irradiation, which resulted in efficient decarbonylation and the formation of the reactive ten-membered-ring enediyne **132** (*Scheme 9*). The latter underwent BC in ^{i}PrOH with a $t_{1/2}$ value of 12 h at 40° to produce the corresponding tetrahydronaphthalen-1,4-diyl, radical which abstracted H-atoms from the available H-donors ^{i}PrOH to form tetralin **133** (*Scheme 9*). The bicyclic cyclopropenone **131** showed no tendency for BC or for the formation of **132** in the dark.

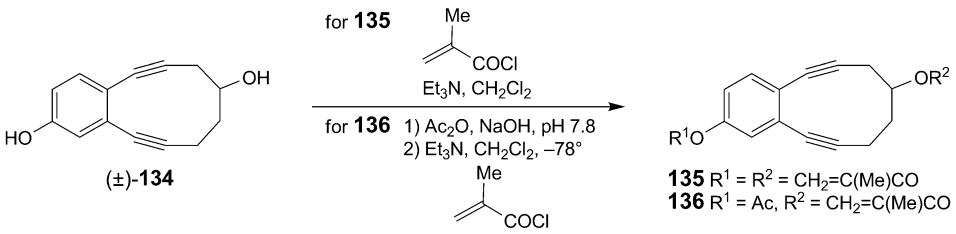
Scheme 9



131 **132** **133**

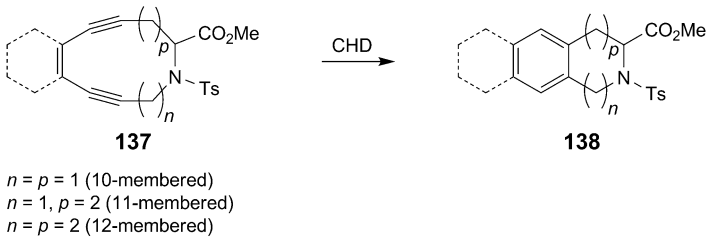
Hickenboth et al. [98] investigated the effects of macroscopic forces on cyclic enediynes **134**–**136** (*Scheme 10*) by using the COGEF (constrained geometries simulating external force) technique to gain insight in BC. Because the forces needed to activate BC were found to be less strong than the forces needed for chain scission in polymer backbones, the calculations indicated that enediynes are potentially useful mechanophores. The authors also synthesized some enediynes, which were evaluated for thermal BC and found to be consistent with the predicted thermal sensitivity based on known substituent effects. Model studies suggested that an insufficient force was applied to the cross-links for mechanical activation to be observable by DSC.

Scheme 10



The syntheses of a series of ten-, eleven-, and twelve-membered enediyne-containing amino acids **137** (*Scheme 11*) were reported in [99]. During the cyclization in several instances, an unexpected (partial) racemization took place, even under virtually neutral *Mitsunobu* conditions. Half-life determination experiments of the enediynes showed that, in line with previous studies, all benzannulated enediynes reacted significantly slower than their unsubstituted counterparts. Moreover, it was evident that ring strain played a major role: An increase in ring size went along with a distinct decrease of the rate of cycloaromatization, best explained by the higher strain

Scheme 11



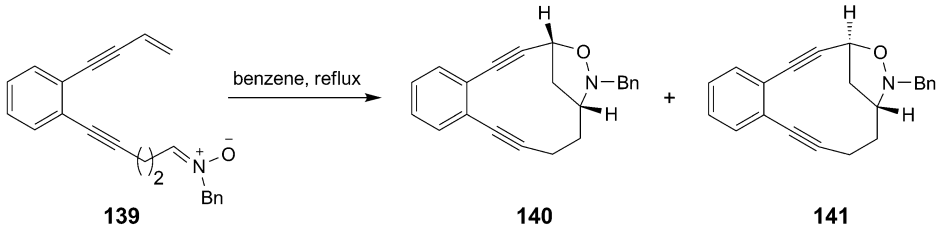
137 **138**

n = *p* = 1 (10-membered)
n = 1, *p* = 2 (11-membered)
n = *p* = 2 (12-membered)

in the smaller ring systems. Among them, ten-membered benzannulated core had the highest potential utility: it is stable at room temperature but can be activated at mildly elevated temperatures.

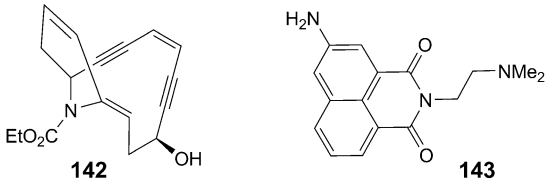
4.2. *Eleven-Membered Enediynes. Basak* and *Ghosh* [100] synthesized bicyclic isooxazolidino fused enediynes **140** and **141** *via* intramolecular nitrone cycloaddition between the two arms of an acyclic enediyne precursor **139** (*Scheme 12*). The reaction was highly regioselective, and the two configurational isomers, **140** and **141**, had similar onset temperatures for BC (*ca.* 200°), indicating no influence of the bridgehead configuration on the kinetics of cyclization, which is in contrast to the observation made by *Nicolaou et al.* [101].

Scheme 12



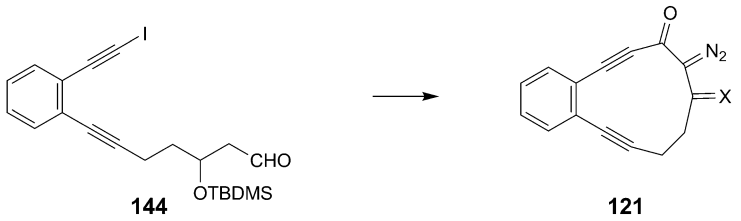
139 **140** **141**

In vitro cytotoxic activities of cyclic enediyne isomers **142** were tested against the highly resistant HT-29 human colon carcinoma [102]. They were found to be 100 times less active than amonafide antitumor agent **143**. Eleven-membered enediyne **121** was synthesized starting from **144** [89] (*Scheme 13*). When solutions containing various concentrations of **121** and supercoiled circular DNA were irradiated at *ca.* −5° at 351 nm using an Ar ion laser, diazo diketone **121** (X = O) induced substantial single-strand cleavage (RF II) of DNA, while the linearized form (RF III) was observed only at higher concentrations of the cleaving agent (> 500 μM) and prolonged irradiation.



142 **143**

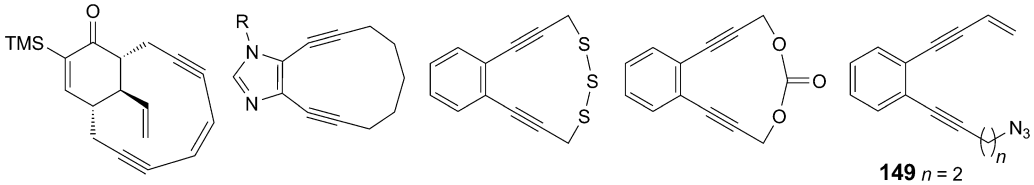
Scheme 13



144 **121**

The relatively high concentrations of **121**, which are required to achieve double-strand DNA photoscission, indicate that **121** has low affinity to a double-strand DNA molecule. To improve the photonuclease activity of enediyne **121**, it should be conjugated with a double-strand DNA minor-groove binding moiety.

A novel eleven-membered enediyne with a bicyclic system, **145**, has recently been synthesized by Cr-mediated dearomatization of 2,6-bis(trimethylsilyl)anisole [103]. This enediyne undergoes BC with a $t_{1/2}$ value of 14.4 h at 142°, while fused enediynes **146** undergo BC photochemically [104]. These imidazole-fused compounds cleave supercoiled plasmid DNA when irradiated with UV light. The imidazole scaffold provides two sites for potential conjugation to biologically important delivery molecules, and thus represents an improvement over known photoreactive benzannulated or heteroatom enediynes, which cannot be simply or directly conjugated. Also, some eleven-membered enediynes containing S- and O-bridges, such as **147** and **148** [105], respectively, were synthesized and characterized spectroscopically.

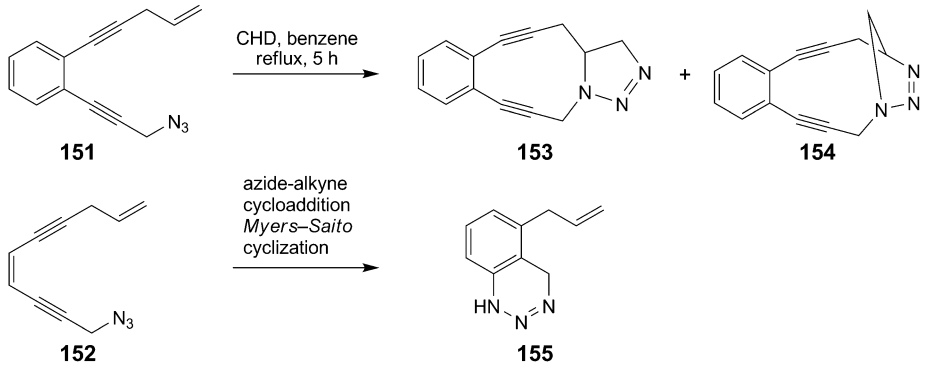


145 **146** R = Me, Bu, Ph **147** **148** **149** *n* = 2 **150** *n* = 3

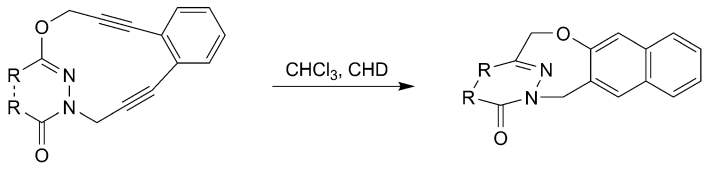
Basak et al. [106] synthesized aromatic azido compounds **149**–**151** and nonaromatic azido enediyne **152** under ambient conditions. The aromatic enediyne **151** underwent the expected cycloaddition with alkene in the neighboring arm to form a stable bridged bicyclic eleven-membered enediyne **154**, but not the expected compound **153** (*Scheme 14*).

4.3. *Twelve-Membered Enediynes.* The structures of twelve-membered 3-oxo-2*H*-pyridazino-fused cyclic enediynes **156** and **157** (*Scheme 15*) [107] were determined by X-ray crystallography. Interestingly, these molecules undergo BC at different rates. BC was studied both in the solid state and in solution. The onset temperature for BC in the solid state of **157** was 228°, and 196° for enediyne **156**. Thus, the enediyne lacking unsaturation at C(4) and C(5) of the parent heterocyclic ring has a lower activation barrier when heated in a neat state.

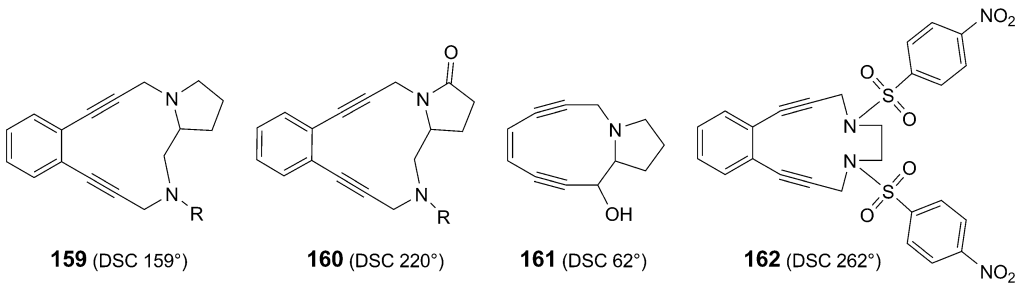
Scheme 14



Scheme 15



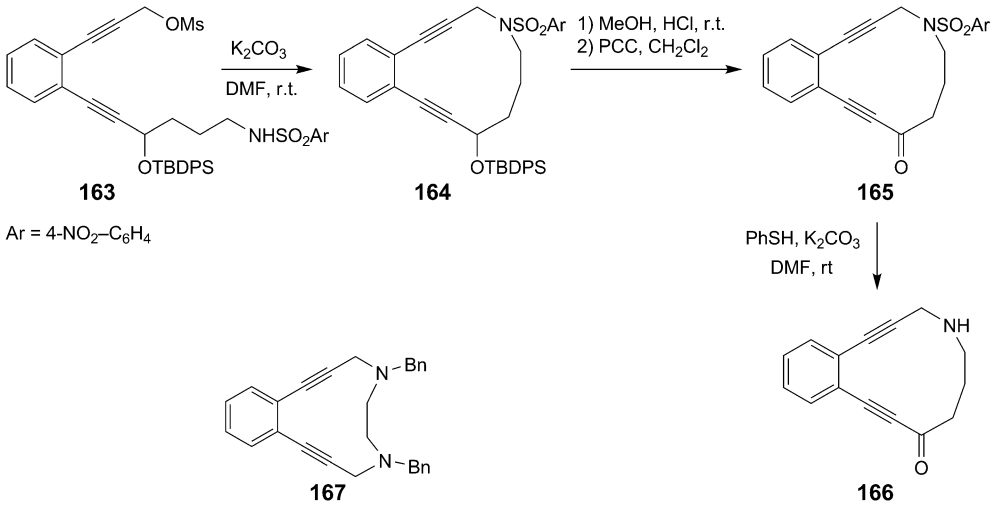
Roy and *Basak* reported twelve-membered bicyclic enediynes **159**–**162** with integrated pyrrolidine and pyrrolidinone moieties [108].



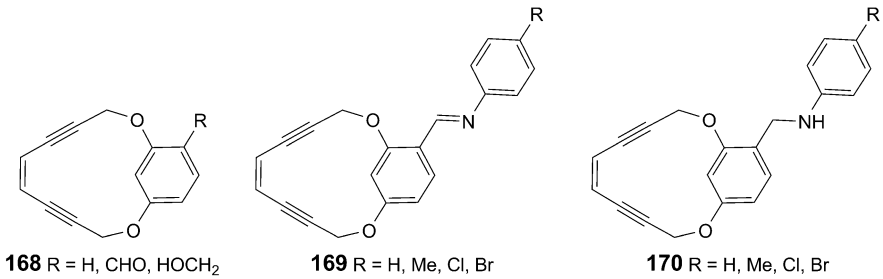
Thermal reactivity data clearly indicated that fusion of five-membered rings like pyrrolidine or oxo-pyrrolidin reduces the onset temperature for BC. Enediyne **164** was accessible *via* intramolecular *N*-alkylation under high dilution [109], and it was further converted to the oxo enediyne **165** (*Scheme 16*). On deprotection of the sulfonamido group of **165**, the aza-ketone **166** was formed. This enediyne proved to be stable at room temperature, and no significant decomposition was observed when a solution of **166** in $CHCl_3$ was kept at 37° for 7 d. Moreover, enediyne **166** could be converted back to the starting sulfonamide **165** upon the treatment with 4-nitrobenzenesulfonyl chloride and

Et_3N, thus demonstrating the inherent stability of **166**. Attempts to induce transannular cyclization with catalytic amounts of TsOH also failed. Some of these compounds underwent BC and cleaved the DNA. Furthermore, enediynes having N-atoms as a part of the ring, *e.g.*, **167**, were stable and underwent BC only at 210° (*Scheme 16*) [110].

Scheme 16



4.4. *13- and 14-Membered Enediynes.* The enediyne **168** were synthesized and screened by *Joshi et al.* [76b][111], who found them to be potent antimicrobially active against *Gram*-positive and *Gram*-negative strains with following results: **168** (R = H): 4 μg/ml against *E. coli* (ATCC 25668), 8 μg/ml *S. typhimurium* (clinical isolate); **168** (R = CHO): 8 μg/ml against *S. aureus* (clinical isolate); **168** ($R = HOCH_2$): 8 μg/ml against *E. coli* (ATCC 25668) and 4 μg/ml against *S. aureus* (clinical isolate). At the same time, the (phenylamino)methyl- and (phenylimino)methyl-substituted cyclic enediynes **169**–**170** were synthesized. In case of **170** (R = Me or H), single-digit (μg/ml) activity against some bacterial strains was detected. Without the enediyne ring, the resorcinol derivatives **171** and **172** (*Fig.*) were found inactive up to 1000 μg/ml against the same bacterial strains. Thus, one can assume that the antibacterial activity of these cyclic enediynes is due to the presence of enediyne core (*Fig.*) and not to the resorcinol part.



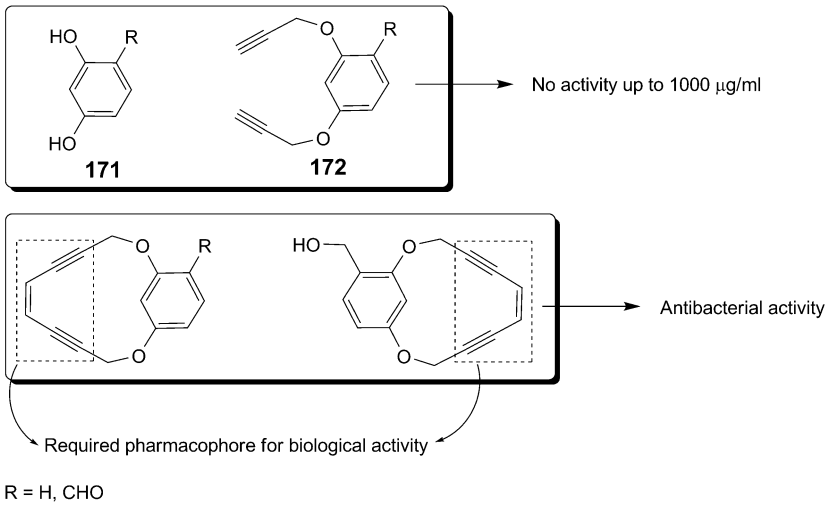
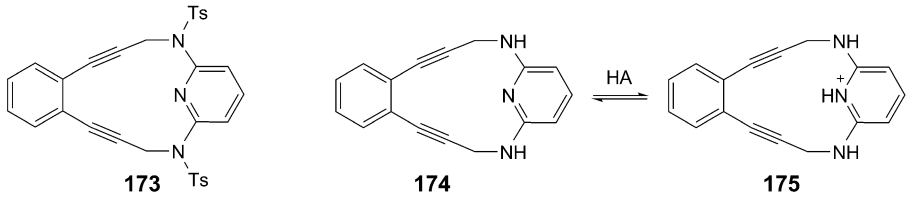


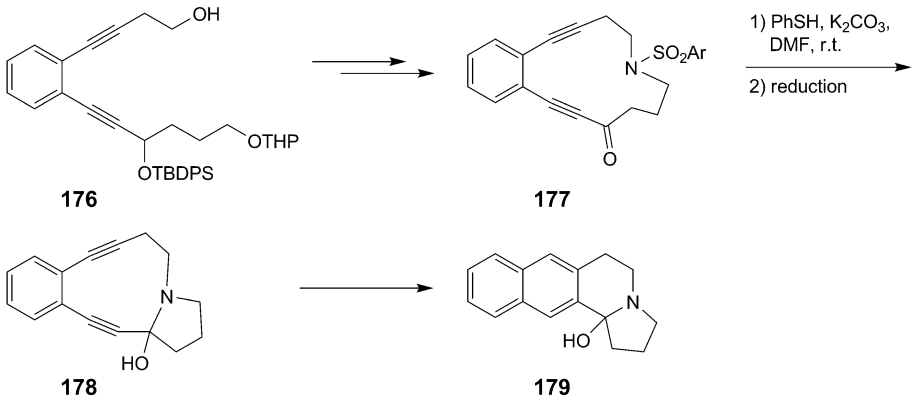
Figure. *Required chromophore for antibacterial activity*

The 13-membered enediynes with an integrated pyridine-2,6-diamino moiety, **173**–**175**, were described in [112]. Thermal-reactivity studies indicated a dependence of the reactivity upon the extent of salt formation with organic acids. This observation is particularly useful for pH-based drug design. It was observed that, by varying the pK_a of the acid, a change of the activation temperature of the enediyne can be achieved. This may have implications in the design of pH-based potent anticancer agents. The onset temperature for BC, for the variety of salt-enediyne **175** was between 214–232°, which was quite similar to **174** with an onset temperature of 234°.

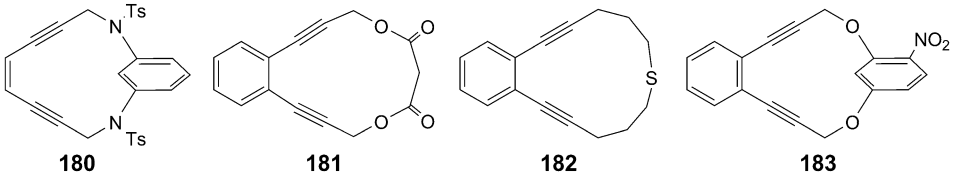


Fused 13-membered azaenediynes **177** have been prepared in several steps [113], which gave the ten-membered fused enediyne **178** at room temperature (*Scheme 17*), which further decomposed in $CHCl_3$ at 4° to afford the cyclized product **179** *via* the corresponding biradical intermediate. Compound **178** led to single-strand cuts when incubated with double-stranded plasmid DNA (pBR 322) in the supercoiled form, while **177**, under similar conditions, did not cause any DNA damage. However, when **177** was incubated with supercoiled DNA in the presence of glutathione, a biological thiol, at a pH of 8.0, the supercoiled DNA was cleaved.

Scheme 17



Some bridged 13-membered enediynes, **180**–**183**, have been synthesized, and the BC tendencies of these compounds have been reported [46][105][114].

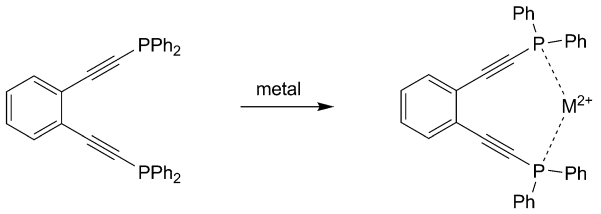


5. Metallo-enediynes. – The use of metals to promote BC has been one of the attractive research activities in recent years [21][22]. The use of cisplatin in the treatment of cancer has opened a door for metals to be used in the treatment of infectious diseases. *Buchwald* and co-workers [115] and *König et al.* [116] hypothesized that enediyne cyclization temperature can either be increased or decreased by the right choice of metals. Both groups demonstrated that indeed BC can be modulated by the use of metals.

5.1. *Pd/Pt/Hg–Enediynes.* In 1995, *Buchwald* and co-workers [115] reported that the dppeb ligand **184** (*Scheme 18*) underwent BC at 243°. However, upon complexation with Pd^{II} and Pt^{II}, the resulting metal–enediyne complexes underwent BC at a much lower temperature (*Scheme 18*). Molecular mechanics calculation at MMX force-field level revealed that the distance between the alkyne termini was decreased from 410 pm in **184** to 330 pm in **185** or **186**.

Similarly, *König et al.* [26] showed that the bipyridine ligand **187** underwent BC at 237°, while, upon complexation with Hg^{II}, the resulting complex **188** cyclized at much lower temperature. The authors postulated that, due to steric hindrance, the free bipyridine ligand exists in a '*transoid*' form **187**, and the alkyne termini are out of plane, while, upon complexation with Hg^{II}, the ligand adopts a '*cisoid*' form **188** which brings

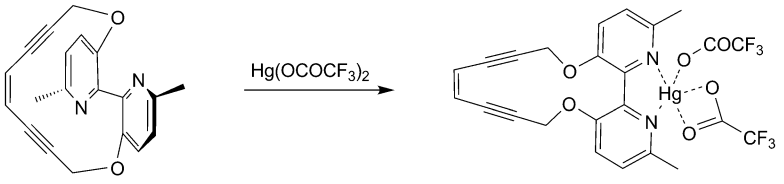
Scheme 18



184 (DSC 243°)

185 M = Pd (DSC 61°)
186 M = Pt (DSC 81°)

Scheme 19



187 (DSC 237°)

188 (DSC 145°)

the alkyne C-atoms 'in plane'. So, a change of molecular geometry by metal complexation leds to lower temperature for the BC (*Scheme 19*).

An elegant study was performed by *Zaleski* and co-workers [22][117] on metallo-enediynes, who also published the first crystal-structure analysis of a metallo-enediyne. Solid-state thermolysis of **189** induced BC at 222° (*Scheme 20*). The thermal reactivity of **189** is very interesting, since complex **185** undergoes BC already at 61°, despite the fact that both complexes have the same ligand (*c.f. Scheme 18*). The main difference between the two complexes is the oxidation state of Pd, namely II in **185** and 0 in **189**. This was the first evidence that the oxidation state of the metal can also influence BC.

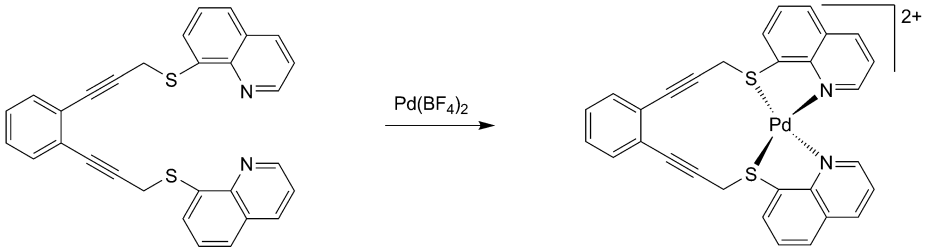
Scheme 20

189

190

Zaleski and co-workers reported also the synthesis of Pd^{II} metallo-enediynes with S- and N-atoms as binding sites [118]. The BC temperature for **191** was determined as 230°, while, on complexation with Pd^{II}, the resulting metallo-enediyne complex **192** cyclized already at 190° (*Scheme 21*). The unusual order in the thermal reactivities of these constructs have been attributed to a *trans*-to-*cis* geometric rearrangement in the square planar arrangement of the complex prior to BC.

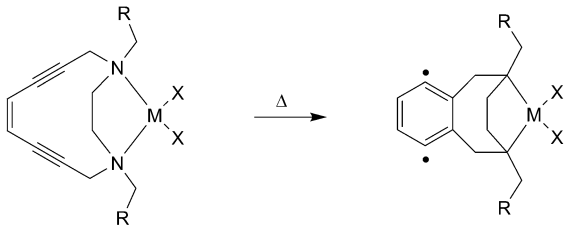
Scheme 21



191 (DSC 230°) **192** (DSC 190°)

Electronic and geometric effects of enediynes also play a major role in the BC. They can be attributed to ancillary metal ligands and steric interactions with ligand substituents. A series of novel metallo-endiyne complexes has been prepared by *Bhattacharyya et al.* [119], who reported on the geometric contributions to BC activation energies derived from metal-induced conformational changes of the ligand (*cf.* **193**, *Scheme 22*).

Scheme 22



193 [$LRMX_2$] **194**

L = enediyne ligand, R = Ph or Me, M = metal, X = halogens

Two trends are recognizable in the thermal reactivities of these metal enediynes: the electronic contributions of ancillary ligands (geometric and electronic) and intraligand functionalities can markedly affect thermal reaction barriers *via* electron repulsion, and steric interactions along the cyclization-reaction coordinate may be important for the observed reaction temperatures. Together, these chemical parameters can have a marked impact on the BC chemistry. Two distinct types of constructs were obtained: the Zn^{II} complexes were tetrahedral, Cu^{II} and the Pd^{II} complexes were all distorted- or square-planar. All tetragonal Cu^{II} species exhibited BC temperatures between 140° and 150° in the solid state, while the square-planar Pd^{II} analogs possess similar critical distances, but cyclized at significantly higher temperatures (205–220°); and for Zn^{II} complexes the temperatures also varied (144–200°; *Table 3*). Moreover, for the planar constructs, the R group has little influence on the cyclization temperatures; however, for the tetrahedral $ZnLX_2$ complexes, the steric bulkiness of the R group plays a more significant role in the cyclization reaction.

A density-functional theory (DFT) study of the electronic perturbations induced by ancillary halogen ligation within the metallo-enediyne constructs **195**–**203** [120][121],

Table 3. *Solid-State* Bergman *Cyclization Temperatures of Metal–Enediynes Complexes*

Compound [LMX_2][a])	R	Cyclization temp. [°]	Distance between the alkyne termini [pm]
L	Ph	170	390
L	Me	168	
[Cu(L)Cl_2]	Ph	141	376
[Cu(L)Cl_2]	Me	136	374
[Cu(L)Br_2]	Ph	148	388
[Zn(L)Cl_2]	Ph	207	375
[Zn(L)Br_2]	Ph	154	374
[Zn(L)I_2]	Ph	144	
[Zn(L)Cl_2]	Me	194	
[Zn(L)Br_2]	Me	200	
[Zn(L)I_2]	Me	196	382
[Zn(L)I_3]	Ph	199	397
[Pd(L)Cl_2]	Ph	225	382
[Pd(L)Cl_2]	Me	207	
[Pd(L)Br_2]	Ph	212	388
[Pd(L)I_2]	Ph	196	386

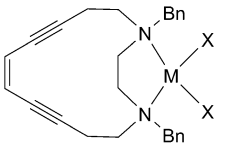
[a]) L represents the enediyne ligands depicted in *Scheme 22*.

and the subsequent effect upon thermal BC temperatures provided further insight. To isolate electronic from geometric parameters of the BC thermodynamics, model Mn^{II}, Cu^{II}, Zn^{II}, and Pd^{II} complexes of diamino and diphosphino enediynes were examined.

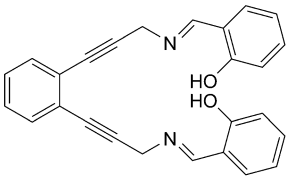
5.2. *Cu/Ag/Zn/Ni–Enediynes. Basak et al.* [122] reported the synthesis of the bis[salicylaldimino] enediyne **204** in three steps. Compound **204** underwent BC at 137°. Complex formation of the imino enediyne **204** with Ni^{II} and Cu^{II} salts afforded new metallo-enediynes **205** and **206**, respectively. The BC onset temperatures for **205** and **206** were 220 and 225°, respectively. The metal in the center of **205** and **206** probably forces the acetylenic C-atoms to move away from each other, thus raising the activation barrier for BC.

Zaleski and co-workers [123] demonstrated that the oxidation state of a metal can substantially influence the BC of the complexed enediynes. They prepared the enediyne ligand **207** (bpod) and, on complexation with Cu^{I} and Cu^{II}, the resulting copper metallo-enediynes **208** and **209**, respectively, which underwent BC at 203 and 152°, respectively. The authors stated that **208** exhibited tetrahedral geometry, and, as a result, the distance between the alkyne C-termini increased, thus leading to an also increased BC temperature of 203° for the Cu^{I} metallo-enediyne. On the other hand, the Cu^{II} complex **210** adopted a square-planar or an octahedral geometry, and, as a result, the distance between alkyne C-termini decreased with concomitant lowering the BC temperature to 121°. By UV studies, the geometry of **210** was determined to be square-planar. In a related study, the authors claimed that rigid enediynes have substantial influence on metal-center geometry [124].

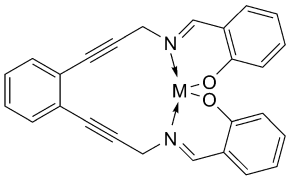
The authors also prepared rigid pyridin-3-yl-substituted enediynes, *e.g.*, **211**, which, on complexation with Cu^{II} and Cu^{I}, gave complexes **212** and **213**. The BC took place at 156° (for **212**) and 326° (for **213**), whereas the acyclic enediyne **211** cyclized at 194°. It



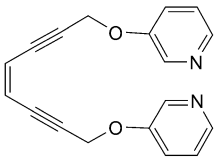
195 M = Zn, X = Cl **196** M = Zn, X = Br **197** M = Zn, X = I
198 M = Cu, X = Cl **199** M = Cu, X = Br **200** M = Cu, X = I
201 M = Pd, X = Cl **202** M = Pd, X = Br **203** M = Pd, X = I



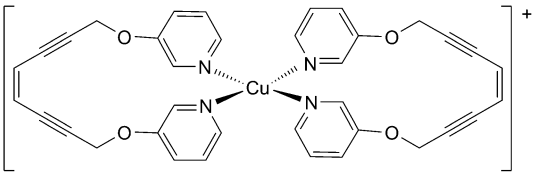
204 (DSC 137°)



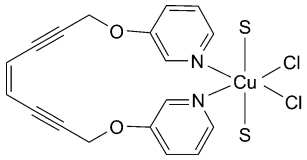
205 M = Ni (DSC 220°)
206 M = Cu (DSC 225°)



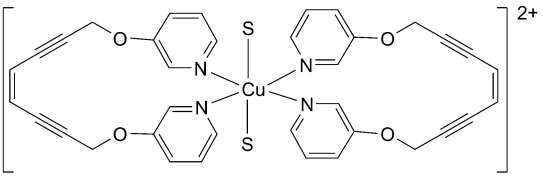
207 (DSC 245°)



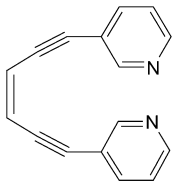
208 (DSC 203°)



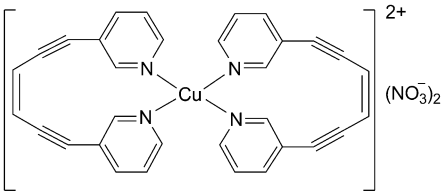
209 (DSC 152°)



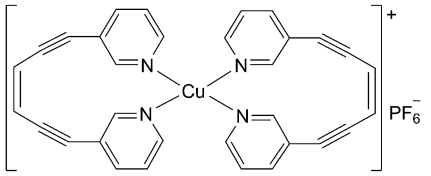
210 (DSC 121°)



211 (DSC 194°)



212 (DSC 156°)



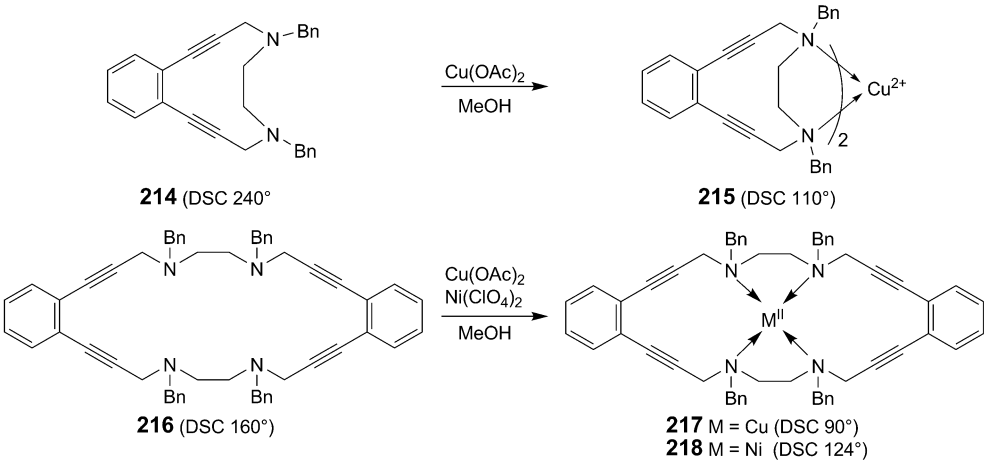
213 (DSC 326°)

should be mentioned that the mere change of the oxidation state of the metal center can lead to a cyclization temperature difference of 170° [122].

Basak et al. [125] synthesized the diaza-enediyne **214** and tetraaza-enediynes **216** (*Scheme 23*). These compounds after complexation with Cu^{II} and Ni^{II} salts afford metallo-enediynes **215**, **217**, and **218** (*Scheme 23*), which underwent BC at much lower temperatures than the free enediyne ligands.

The 24-, 26-, and 28-membered macrocyclic enediynes **219**, **223**, and **220**, respectively, and their metal complexes **221**, **222**, **224**, and **225** have also been reported [126]. Again, the macrocyclic enediyne–metal complexes exhibited lower BC temperatures than the corresponding macrocyclic enediynes. The BC temperatures of the

Scheme 23



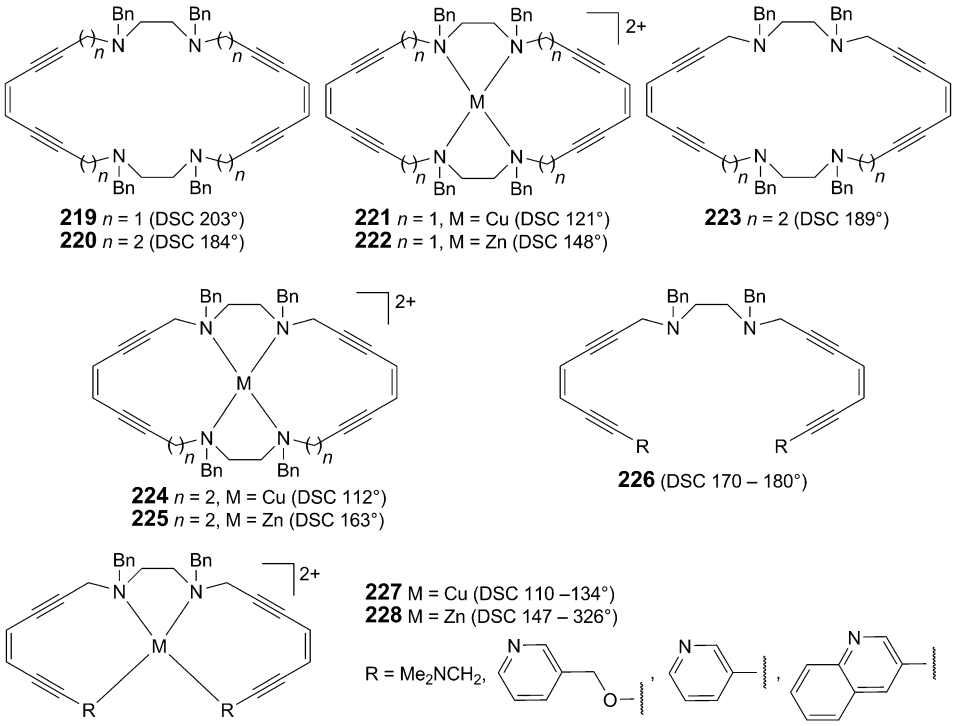
214 (DSC 240°)

215 (DSC 110°)

216 (DSC 160°)

217 M = Cu (DSC 90°)
218 M = Ni (DSC 124°)

macrocyclic enediynes **219**, **223**, and **220** were found to be in the range of 180–203°. The BC temperatures of the macrocyclic metallo-enediynes **221** and **222**, on the other hand, were 121° and 148°, respectively. The higher temperature for **222** was between those expected for a planar or tetrahedral structure. For complex **224**, a modest decrease in



219 *n* = 1 (DSC 203°)
220 *n* = 2 (DSC 184°)

221 *n* = 1, M = Cu (DSC 121°)
222 *n* = 1, M = Zn (DSC 148°)

223 *n* = 2 (DSC 189°)

224 *n* = 2, M = Cu (DSC 112°)
225 *n* = 2, M = Zn (DSC 163°)

226 (DSC 170 – 180°)

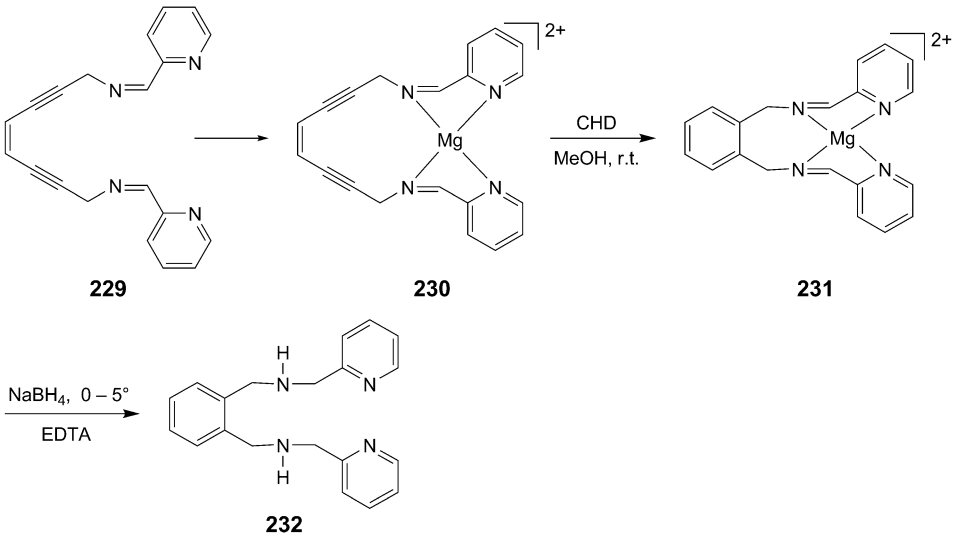
227 M = Cu (DSC 110 –134°)
228 M = Zn (DSC 147 – 326°)

R = Me_2NCH_2,

the cyclization temperature of 9° was observed relative to that of **221**, which is structurally quite similar and which must possess planar-to-tetragonal geometries about the metal center. The BC temperature of **225** was 163°, which is 15° higher relative to that of **222**. Thus, in Zn^{II} metallo-enediyne, a distortion from planarity for four-coordination resulted in a tetragonal geometry. Tetradentate acyclic enediynes and their metal complexes have also been reported [126]. The BC temperatures for **226** with the different R and R′ groups were between 170–188°. Metallation of these compounds resulted in **227** (Cu^{II}) and **228** (Zn^{II}). The complexes of **227** underwent cyclizations at much lower temperatures (110–134°) than **228** (147–326°).

5.3. *Mg–Enediynes.* Their enhanced thermal reactivity of the tetradentate metallo-enediyne complexes with Cu^{II} and Zn^{II} was controlled by ligand design and metal geometry. However, the thermal barriers are still too high for biological application. Therefore, *Zaleski* and *Rawat* [127][128] synthesized a Mg^{II}–enediyne complex, which cyclized efficiently in solution at ambient temperature (*Scheme 24*). There are a very limited number of enediynes which undergo cyclization at ambient temperature. Diimino enediyne **229** was synthesized starting from diamino enediyne **63**. The thermal reactivity of **229** was astonishing in the presence of metal ions [127]. Addition of $Zn(OAc)_2$ or $Cu(OAc)_2/Cu(NO_3)_2$ to the stirred solution of the ligand **229** led to immediate change in the color of the reaction mixture from light brown to black. ^{1}H-NMR Spectrum of the mixture recorded immediately after addition of a Zn^{II} salt exhibited only resonances for the polymerized or decomposed product, indicated by a broad resonance in the aromatic region. Interestingly, when **229** was reacted with $MgCl_2$ at 0°, Mg-complexed enediyne **230** was obtained and characterized spectroscopically, which, on stirring at room temperature in MeOH, again yielded polymeric materials. However, using CHD as radical scavenger, **230** underwent BC at room

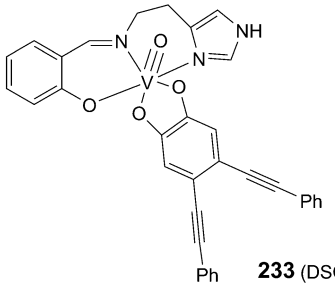
Scheme 24



229 **230** **231** **232**

temperature. The cyclized product **231** was characterized after reduction to **232** by comparing the spectral data of the latter with those of an authentic sample.

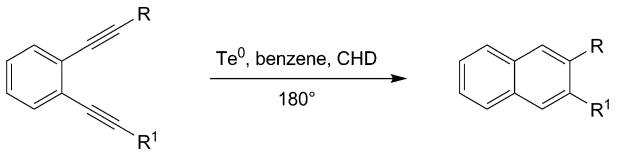
5.4. *V–Enediyne. Zaleski* and co-workers [129] also synthesized the V^V–enediyne complex **233**. *Raman* and DSC data showed that the LMCT (ligand-to-metal charge transfer) transitions can be used to photo-thermally activate the complex **233**. BC at 785 or 1064 nm laser excitation produced insoluble polymeric materials despite the compound's relative inertness to photo-*Bergman* reactivity upon electronic excitation in the UV-spectral region.



233 (DSC 246°)

5.5. *Te–Enediynes. Anthony* and co-workers [130] reported that the cyclization of enediynes **234** to fully aromatized 2,3-substituted naphthalenes can be achieved by the use of Te^0 (*Scheme 25*). Reaction of stoichiometric Te^0 with the enediynes resulted in the formation of the cyclized products **235**. In 1991, *Tsuchiya* and co-workers [131] attrumpted the synthesis of benzotellurepines by hydrotelluration of an enediyne. While the expected benzotellurepine was indeed formed in good yield, the major decomposition product was naphthalene.

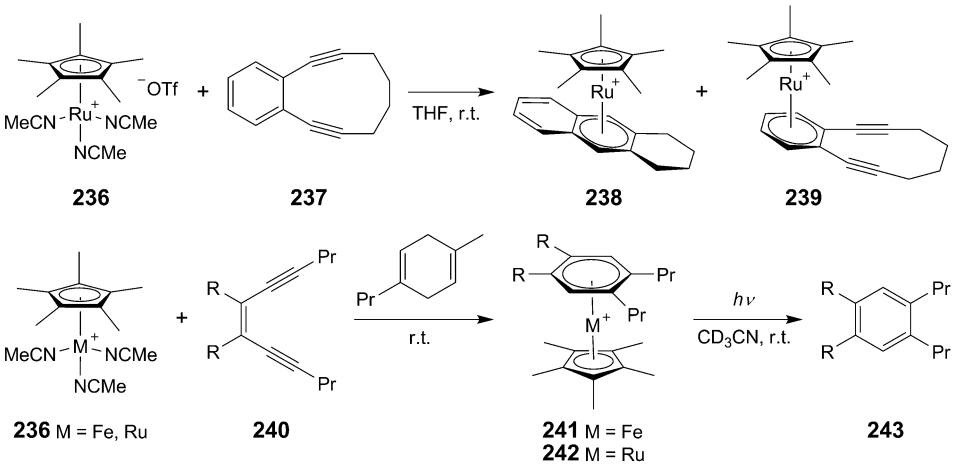
Scheme 25



234 **235**

5.6. *Ru/Fe–Enediynes. O'Connor et al.* [132][133] reported Ru–arene–enediynes, and used a fundamentally different cyclization trigger which involved the room temperature reaction of $[(\eta^5\text{-}C_5Me_5)Ru(MeCN)_3]OTf$ with either benzannulated or alicyclic enediynes without heteroatoms [133]. The reaction of **236** with **237** led to the formation of a small amount of cyclized product **238** along with non-cyclized Ru–arene–enediyne **239** as the major product (*Scheme 26*). These results led to the development of Fe–arene complexes **241** as air-stable reagents for the room-temperature cycloaromatization of enediynes (*Scheme 26*) [134].

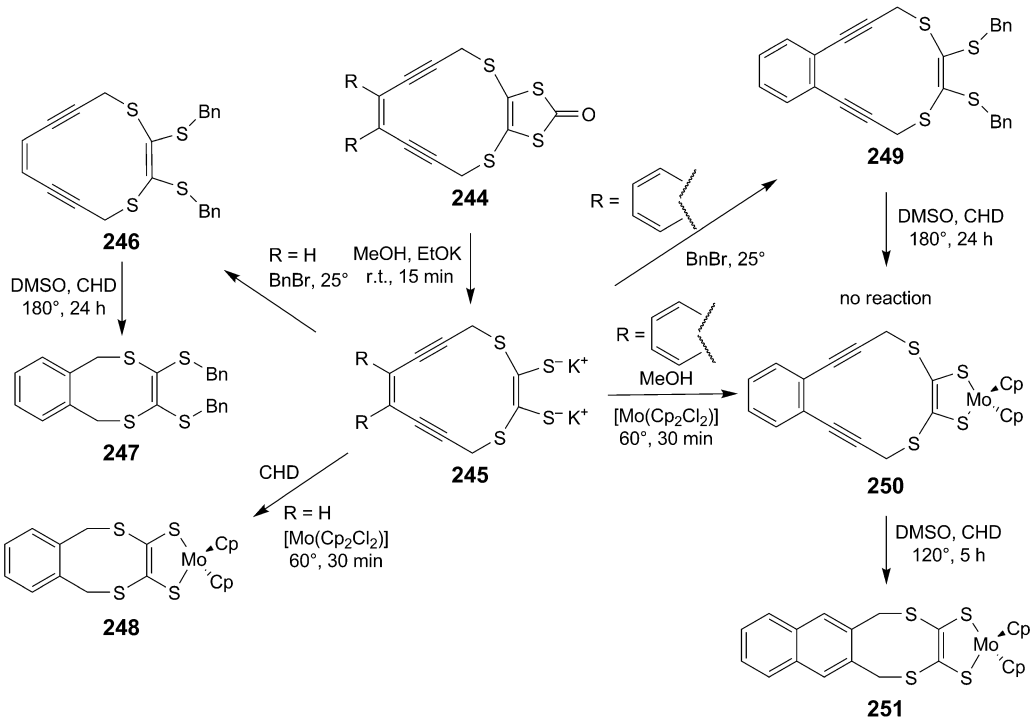
Scheme 26



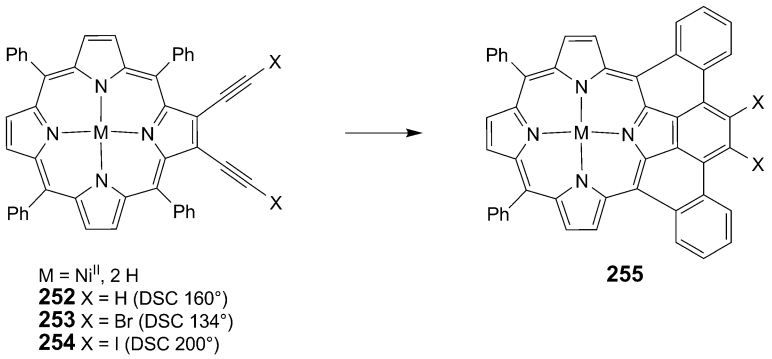
5.7. *Mo–Enediyne. Zaleski* and co-workers [135] also reported on the synthesis of thia-based metallo-enediynes (*Scheme 27*) and demonstrated that high-valent metals can be effective cofactors for enediye activation through electronic rather than geometric influences. Enediyne **244** was stable in solution and did not cyclize upon heating even up to 180° in DMSO/CDH 1:100 over 24 h. The dithiolate **245** was stable at ambient temperature in MeOH under N_2 atmosphere for 3 h as well as at 80° for 1.5 h prior to slow decomposition to non-*Bergman* side products. Heating of **245** (R = H and CH=CH–CH=CH) in the presence of the Mo^{IV} complex in MeOH at 60° for 30 min afforded **248** (R = H) and **250** (R = CH=CH–CH=CH) as metal centered enediynes, respectively. Compound **248** consisted of some insoluble polymeric materials, while, at low temperature, no complex was formed. Compound **250** cyclized at 120°/5 h in DMSO/CHD and afforded **251** with a major part of unreacted **250**. The X-ray structure analysis confirmed that compound **248**, **250**, and **251** possessed pseudo-tetrahedral structures. To evaluate whether σ-coordination or π-complexation prompted the cyclization, **245** was converted to **246** and **249**, respectively. Enediyne **246** was notably stable and required a cyclization temperature of 180° to form slowly **247**, whereas no reaction took place in form of the Mo^{IV} complex **248**. These findings disqualified a π interaction between the enediyne fragment and Mo^{IV} as the origin of enediyne activation for BC. Similarly, **249** also did not undergo cyclization. Mo^{IV}–Enediyne complexes **248** and **251** showed characteristic S→Mo^{IV} LMCT transition between 500 and 535 nm.

5.8. *Porphyrin–Enediyne Conjugates.* The *Bergman* cyclization of diethynylporphyrin **252** (*Scheme 28*) exhibited a double activation barrier for the formation of BC products [136]. Addition of an H-atom acceptor such as DDQ accelerated the formation of the picenoporphyrin, indicating that the second barrier was rate determining. To address these issues, *Zaleski* and co-workers [137] prepared the free base 2,3-diethynyl-5,10,15,20-tetraphenylporphyrins with TMS or H at the alkynyl termini, and their Ni^{II} complexes. The ambient-temperature activation of **253** can be

Scheme 27



Scheme 28

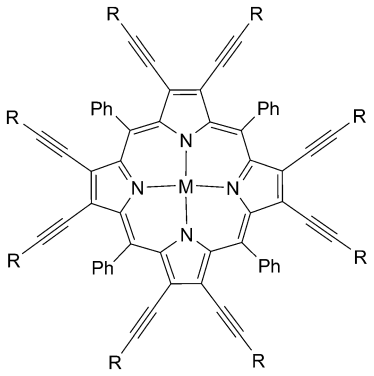


rationalized by the ability of σ-acceptor substituents at the alkyne C-termini to lower the activation barrier for BC product formation.

In the present case, the reduction in the barrier for Br relative to I or H substitution was remarkable, and led to a unique example of an uncatalyzed, ambient-temperature BC of an acyclic enediyne fused to an aromatic system. These results contributed

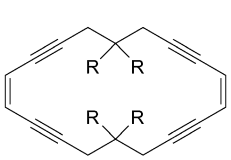
significantly to the broader field of activation and control of diradical reactivity, which is important for future biomedical applications or material science.

Zaleski and co-workers [138] synthesized a series of porphyrinic enediynes, **256**–**258**, and most of these compounds were characterized by X-ray crystallography. Thermal and photochemical reactivity of the octakis-substituted free-base derivative led to the same 5,15-dihydroporphyrin product, indicating that the thermal and photochemical reaction pathways are connected by a common product. These results revealed key criteria required for the design of second-generation porphyrinic enediyne structures with specific reactivities.

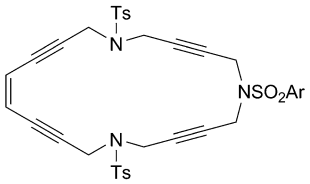


256 M = Ni, R = Ph
257 M = 2 H, R = Ph
258 M = 2 H, R = Me_3Si

6. Macrocyclic Enediynes. – *König et al.* [35] synthesized the 18-membered macrocyclic enediynes **259**–**261**. The thermal stability of **259** was determined by DSC. An irreversible exothermic reaction was observed at 177°, which was explained by



259 R = CO_2Et
260 R = CN
261 R = Ac



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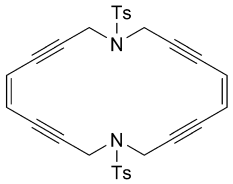

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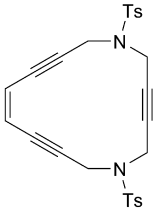

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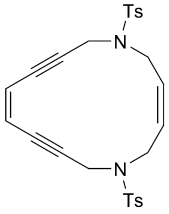
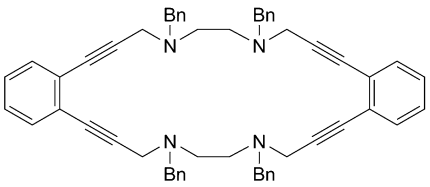


264



265

thermally induced cyclization of the enediyne moieties, followed by bulk polymerization. X-Ray structure analyses revealed chair and twisted conformations of the macrocycles **260** and **261**, respectively, in the crystal.

Gonzalez et al. [139] also synthesized several 14- and 19-membered macrocyclic sulfonamides of diaza-enediynes. These molecules were characterized spectroscopically as well as by single-crystal X-ray diffraction analysis. These macrocyclic enediynes **262**–**264** underwent BC in solid state. However, no BC products were isolated when the compounds were heated in toluene at 90–100° for 24 h.

Basak et al. [125] synthesized the macrocyclic aza-enediynes **265** and **266** by multiple-step syntheses. These aza-enediynes were used for the preparation of well-defined complexes. Heating of **265** in PhCl in presence of CHD led to the disappearance of the starting material, and a complex mixture of cyclized products was formed. The fluorescence spectra of **265** in DMSO showed extremely weak excitation and emission at λ_{max} 360 and 426 nm.

Recently, two new carbon-rich macrocycles, with bis-enediyne cores, were synthesized by *Gholami et al.* [140]; they were named radioannulenes. These compounds possess unsaturated carbon frameworks that are intermediate between those of linearly conjugated dehydro-benzannulenes and cross-conjugated expanded radioannulenes.

7. Conclusions. – In this review, we tried to compile recent developments in enediyne chemistry. As natural enediynes were known for their antitumor, antimicrobial, and cytotoxic activities, the work also includes synthetic enediynes and their thermal behavior. Most of natural enediynes are in clinical trials. The synthesized enediynes were well-characterized for their highly potent antitumor, antimicrobial, as well as cytotoxic activities. Also several metallo-enediynes were synthesized, to understand how geometry, oxidation states, electronic factors, and steric bulk at the ene- and yne-C-atoms influence distance between the alkyne termini, which plays a major role for the BC.

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