Antineoplastic

Their antineoplastic effect is manifested by suppressing malignant cell proliferation, stimulating apoptosis, inhibiting the action of a series of enzymes, and activating macrophages.

From: Advances in Protein Chemistry and Structural Biology, 2015

Related terms:

Protein, Ligand, Doxorubicin, Nanoparticle, Platinum, Cisplatin, Antitumor, Antineoplastic Agent

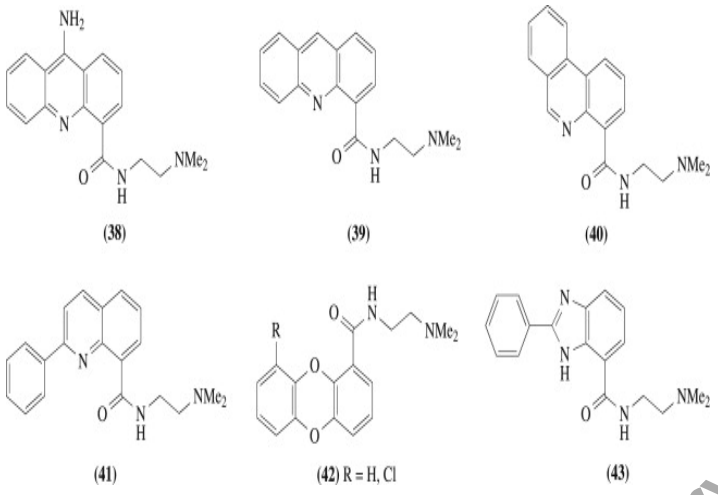
DNA and Aspects of Molecular Biology

Timothy L. MacDonald, ... Jetze J. Tepe, in Comprehensive Natural Products Chemistry, 1999

7.16.3.3.2 "Minimal" intercalative agents

The antineoplastic activity of the acridine derivatives resulted in extensive efforts to refine their pharmacological profile further. While initial attempts focused on increasing the efficiency of DNA intercalation, it became apparent that there was a problem associated with correlating *in vitro* binding affinities with *in vivo* cytotoxicity for most analogues of this family. The problem was believed to result from the failure of the drug to be transported efficiently to the nucleus, the site of action of the drug. It had been demonstrated that some molecules with large binding constants were unable to be distributed to sites which were remote from the site of administration. Problems with drug distribution may be overcome in some cases by improving water solubility (e.g., amsacrine • HCl vs. CI-921 • HCl, 0.12 mg ml^{-1} vs. 0.72 mg ml^{-1}).[129] However, increased hydrophilicity must be balanced against the hydrophobicity required to diffuse successfully through the lipophilic membrane structure. Membrane penetration generally occurs by the neutral species when ionizable functionalities are present; thus, the difference in pK_a between amsacrine (pK_a = 7.43) vs. CI-921 (pK_a = 6.40) results in a 10-fold concentration advantage for the uncharged CI-921 species at physiological pH.[129] Additionally, because the distribution into tissue will take place by passive diffusion, the magnitude of the diffusion constant for molecules will critically affect their ability to reach an intracellular target. Molecules with large diffusion constants will have difficulty reaching their nuclear target. These problems have led to efforts to develop a class of antineoplastic agents, the "minimal" intercalators, which attempt to balance favorable distribution properties with moderate binding affinities. Although these compounds bear a structural resemblance to the broad class of anthracenedione derivatives, they have been treated separately to illustrate rational approaches to overcoming the distribution problems associated with hydrophobic intercalative agents. A variety of structural classes were synthesized to alter both the DNA-binding affinity and the drug hydrophobicity relative to the parent compound 9-aminoacridine-4-carboxamide (**38**). The acridine-4-carboxamides (**39**),[130] and also the angular analogue (**40**)[131] and the "2–1" analogue (**41**),[132] had both lower binding constants and lower pK_a values relative to the parent compound (**38**), while retaining *in vivo* cytoxicity. Additionally, compounds with less aromatic chromophores, including dibenzo[1,4]dioxin-1-carboxamide (**42**)[133] and the phenylbenzimides (**43**),[134] had even lower DNA binding constants and pK_a values, while retaining activity. It should be noted, however, that the mechanism of

cytotoxicity of the "logical conclusion" of this series, the phenylbenzimides (**43**), does *not* appear to involve the stabilization of a topoisomerase II-cleavable complex.



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URL: https://www.sciencedirect.com/science/article/pii/B9780080912837000710

Bioinorganic Fundamentals and Applications: Metals in Natural Living Systems and Metals in Toxicology and Medicine

A.M. Pizarro, ... P.J. Sadler, in Comprehensive Inorganic Chemistry II (Second Edition), 2013

3.25.2.1.2.3 Transplatin analogues

The lack of antineoplastic activity of transplatin and analogues discovered in the early days of platinum-based anticancer research led to withdrawal of interest in platinum complexes with *trans* geometry as possible chemotherapeutics.[195] Almost 20 years after transplatin was discarded on the basis of structure/activity relationships, Farrell and coworkers discovered the cytotoxic activity toward cancer cells of *trans*-platinum complexes different from those synthesized in the early days.[196,197] Their findings for transplatin analogues with aromatic N-donor heterocycles substituting ammonia provided inspiration for further exploration by many other research groups. The first *trans*-platinum complexes with reported cytotoxic activity *in vitro* were *trans*-[$PtCl_2(NH_3)$(quinoline)] and *trans*-[$PtCl_2(NH_3)$(thiazole)]. Their mode of binding to DNA has been elucidated.[198–201] DNA binding of *trans*-platinum complexes in comparison with cisplatin is summarized in **Table 7**.

Table 7. Some DNA-binding preferences of *trans*-diamineplatinum(II) complexes in comparison with cisplatin

Ligands in *trans* positions	Type of DNA adduct			DNA bending	DNA unwinding	Ref.
	Intra (%)	Inter (%)	Mono (%)			

Ligands in *trans* positions	Type of DNA adduct			DNA bending	DNA unwinding	Ref.
	Intra (%)	Inter (%)	Mono (%)			
Cisplatin NH_3 vs. Cl	GG + AG (~ 90)[166] GXG	GG (~ 6)[192]	G	32–34° tmag (1,2)[202–204] 40–45° tmig (ICL)	13° (1,2)[202–204] 76–79° (ICL)	166,192,204
Transplatin NH_3 vs. NH_3	28	GC (~ 12)[192] 1,3-GNG	G, C	20° tmig (ICL)[192]	12° (ICL)[192,193]	166,192,
NH_3 vs. quinolone	GG, AG	GG (30)[200,201]	G		17°	200,201
NH_3 vs. thiazole	1,3-GG (20–40)[200,201]	GG (30–40)[200,201]	G (30–40)[200,201]	40° tmig (1,3)[198] 22° tmig (ICL)[198] 34° tmag (mono)[199]	15° (1,3)[198] 20° (ICL)[198] 12° (mono)[199]	198–200
E-iminoether vs. *E*-iminoether			G[205]	21° tmig[206]		
Dimethylamine vs. (^{i}Pr)NH_2		GC[207,208]				207,208
NH_3 vs. (Me)(Bu)NH		40	36%		8°	209
NH_3 vs. *sec*-Butylamine		50	36%		8°	209
(^{i}Pr)NH_2 vs. 3-OH–Me–Py	GG (69)	10–12	G, A (20)		16°	210
^{i}PrNH_2 vs. 4-OH–Me–Py	GG (64)	10–12	G, A (25)		16°	210
4-Picoline vs. piperidine	GG (92)	3	G (5)			211
4-Picoline vs. piperazine	GG (76)	6	G (18)			211

OH–Me–Py, hydroxymetylpyridine; tmig, toward minor groove; tmag, toward major groove.

Soon after Farrell's work, others exploited the *trans*-Pt geometry finding a number of biologically interesting complexes as, or even more, cytotoxic than their *cis* analogues, and sometimes more than cisplatin itself. For instance, Natile and Coluccia reported complexes containing imino ligands that exhibited potency toward *in vitro* tumor cell growth, often being active toward cisplatin-resistant tumor cells.[212,213] They found that the complex *trans*-[$PtCl_2$(*E*-iminoether)$_2$] formed essentially monofunctional adducts at guanine residues on DNA.[205] They also found that these adducts are not recognized by HMGB1 proteins, but readily crosslink proteins, which markedly enhances their efficiency in terminating DNA polymerization by DNA polymerases *in vitro* and inhibiting removal of this adduct from DNA by nucleotide-excision repair (NER) proteins. They suggested that DNA–

Pt–protein ternary crosslinks are responsible for the antitumor activity of this drug.[206] Navarro and coworkers have developed a series of branched chain amine *trans*-Pt complexes[214,215] with remarkable cytotoxicity.[208,216] Particularly, the DNA-binding properties of the complex *trans*-[$PtCl_2$(methylamine)(isopropylamine)], for which the cytotoxic activity implicates apoptosis, involve mainly interstrand crosslinks between guanine and its complementary cytosine.[207,208] Curiously, a comparison of the *in vivo* activity of the Pt^{II}/Pt^{IV} pair – *trans*-[$PtCl_2(OH)_2$(dimethylamine)(isopropylamine)] and *trans*-[$PtCl_2$(dimethylamine)(isopropylamine)] – showed that only the Pt^{IV} analogue was able to inhibit the growth of CH1 human ovarian carcinoma xenografts in mice. Moreover, binding studies with serum albumin indicated that the platinum(II) complex possesses a much higher reactivity toward albumin than the platinum(IV) complex suggesting that the lack of *in vivo* antitumor activity shown by the former might be related to its extracellular inactivation before reaching the tumor site because of its high extent of binding to plasma proteins, up to 70% of binding after 0.25 h.[217] In contrast to other *trans*-Pt^{II} complexes, complexes with aromatic ligands *trans* to isopropylamine such as *trans*-[$PtCl_2$-(isopropylamine)(3-(hydroxymethyl)-pyridine)] and *trans*-[$PtCl_2$(isopropylamine)(4-(hydroxymethyl)-pyridine)] form largely intrastrand crosslinks.[210]

Finally, Gibson and coworkers have recently developed platinum(II) complexes with planar and nonplanar cyclic ligands in *trans* geometry which are highly cytotoxic toward a number of cancer cell lines.[218–223] Some of the results observed in DNA-binding experiments are striking. The complex *trans*-[$PtCl_2(NH_3)$(pip-pip)]$^+$ (where pip-pip is 4-piperidinepiperidine) (**14**, in **Chart 6**) binds to DNA extremely rapidly (the $t_{1/2}$ for coordination to calf thymus DNA (CT-DNA) is 13 min at 37 °C[224]) and without the complex undergoing initial aquation;[222] the complexes *trans*-[$PtCl_2$(4-picoline)(piperidine)] and *trans*-[$PtCl_2$(4-picoline)(piperazine)]$^+$ (**15** and **16**, respectively, in **Chart 6**) form a high number of intrastrand crosslinks in double-helical DNA, 92% and 76%, respectively, after 48 h.[211]

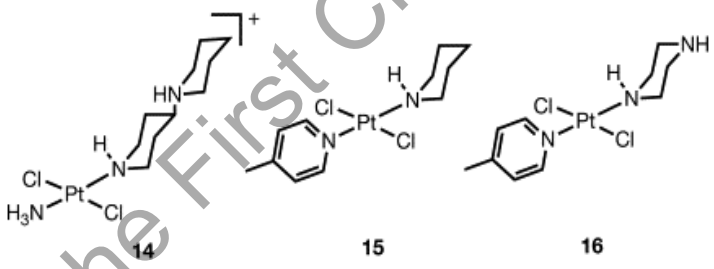

Chart 6. Molecular structures of complexes **14**–**16**.

In summary, substitution of one or more amine ligands in transplatin by aromatic N-donor heterocyclic ligands, branched aliphatic amines, or imino ligands has led to compounds with significant inhibitory potency toward *in vitro* tumor cell growth. These *trans* complexes are often active toward cisplatin-resistant tumor cells and in some cases endowed with significant activity *in vivo*. The DNA-binding characteristics of these *trans*-platinum complexes are different from those of the parent cisplatin, perhaps explaining the lack of cross-resistance; the perturbations of DNA structure are also different from those induced by transplatin itself.

Nevertheless, no *trans*-platinum complex has yet entered clinical trials. Future work will involve understanding why certain *trans*-platinum complexes are active, and sometimes more active than their *cis*-platinum counterparts, often active in cisplatin-resistant cell lines, and the nature of the crucial lesions on DNA. It is also notable that a new family of *trans*-platinum complexes photoactivable in cells has recently shown promise as anticancer agents.[225–231] These complexes have the ability to form unusual adducts with DNA, such as 1,3-intrastrand GNG, interstrand, and DNA–protein crosslinks. The DNA damage appears to be different from that induced by cisplatin or transplatin.

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Bioactive Natural Products (Part E)

Hideji Itokawa, ... Hiroshi Morita, in Studies in Natural Products Chemistry, 2000

Cytotoxic Activity and Antineoplastic Activity

Cell growth and inhibitory effects were examined against KB cells, P388 lymphocytic leukemia cells, and MM2 mammary carcinoma cells by using the lead compound RA-V and *n*-hexyl ether derivative, which had shown the strongest antitumor activity in the *in vivo* assay. The results are shown in Fig. 19. The *n*-hexyl ether showed clear growth-inhibitory effects at concentrations higher than 5×10^{-2} μg/ml and 5×10^{-2} μg/ml, respectively, in KB cells, and 1×10 μg/ml and 1×10^{-1} μg/ml in MM2 cells. Thus the growth inhibitory effect of the *n*-hexyl ether derivative was stronger than that of RA-V in each cell line and showed dose-dependency [86–87].

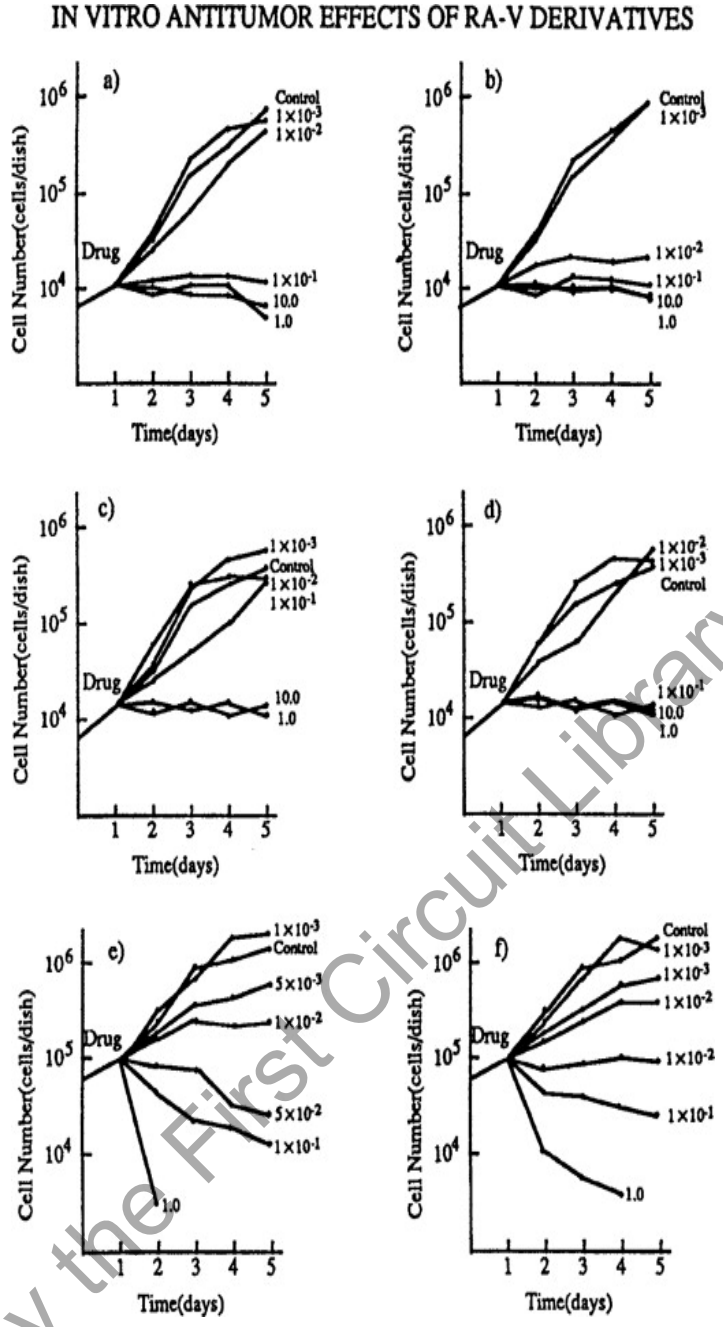
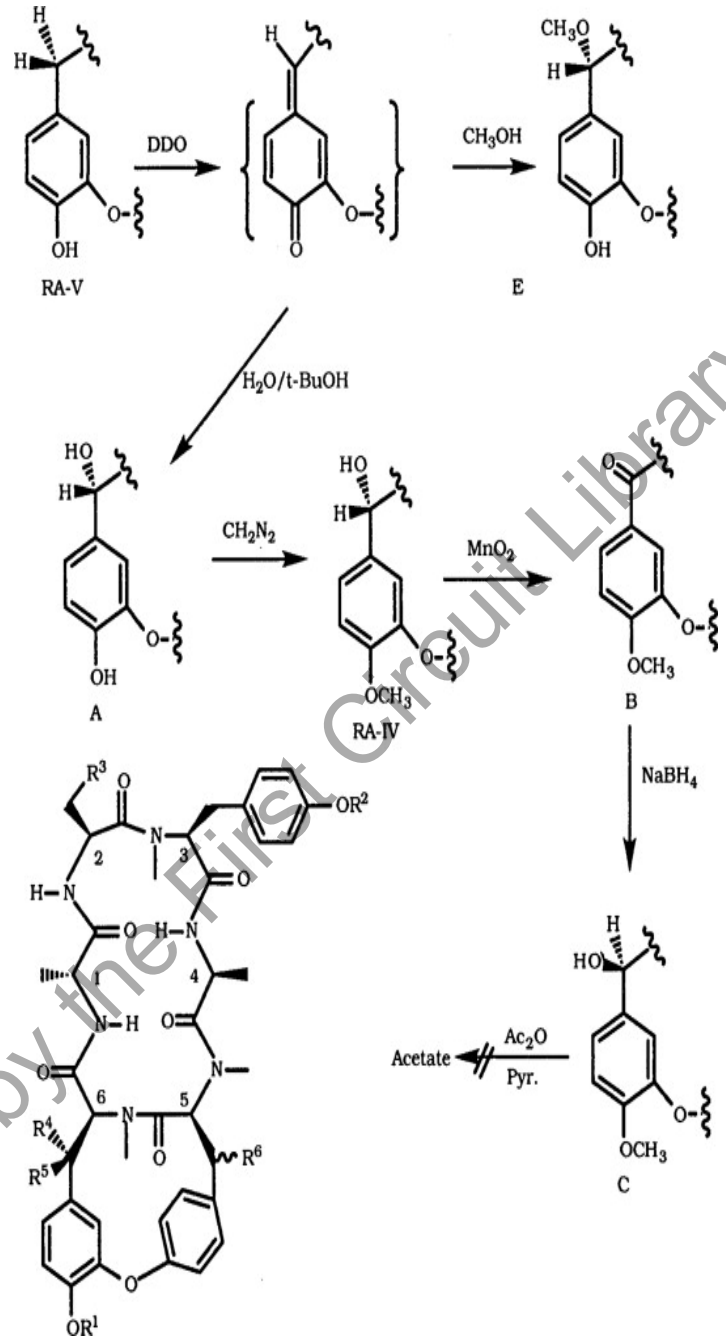


Fig. (19). Effects of RA-V and its n-Hexylether on the growth of P388, MM2 and KB cells. P388 (9.70×10^3, a and b), MM2(1.24×10^4, c and d) and KB cells (1.04×10^5, e and f) were treated with various concentrations of drugs and cell growth was followed daily with a Coulter. Drugs: a, c and e; RA-V. b,d and f; n-hexylether of RA-V.

Microscopically, mitomycin C-treated KB cells showed deformation, and enlargement and abnormality of nuclei, whereas KB cells treated with RA-V and its *n*-hexyl ether derivatives showed globulization as compared with control cells.

RA-IV was considered to have an additional alcoholic hydroxyl group as compared with RA-VII. It was concluded that the hydroxyl group in RA-IV is linked to the β-carbon (β) of Tyr-6 by comparing the ^{13}C chemical shift values of RA-IV with those of RA-VII; Cβ signal at δ 35.56 (t) due to Tyr-6 of RA-VII was shifted down field to 73.49 (d) in RA-IV, while other carbon signals in both peptides were similar. Next, in order to introduce an oxygen functional group into the benzyl position of Tyr-6, RA-V was oxidized with 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) as shown in Chart 4. This reaction gave selectively compound E in methanol and compound A in 90% aqueous tert-BuOH solution. Compound A was methylated with diazomethane to yield RA-IV. In addition, to confirm the configuration of the

hydroxyl group in RA-IV, its epimer (C) was synthesized. This epimer could not be acetylated with acetic anhydride and pyridine at room temperature. These findings can be reasonably explained by the following stereochemical considerations: the reagent in this series of reactions can approach only from the α-side, because the β-side at the benzyl location of Tyr-6 is strongly blocked by the *N*-methyl group of this tyrosine moiety, as noted from the X-ray conformation. Consequently, the hydroxyl group of RA-IV was determined to have an *S* configuration.



(Chart 4).

We also examined the antineoplastic activity of six native cyclic hexapeptides (RA-I, II, III, IV, V and VII) and seven related compounds against P388 lymphocytic leukemia in mice. The mice received 10

Table XIV. Antitumor Activities on P-388 Lymphocytic Leukemia and Toxicities of Ether Derivatives of RA-V

R	T/C (%)				Toxicity[f] Dose (mg/kg					
	0.05 mg/kg	0.5 mg/kg	2.0 mg/kg	4.0 mg/kg						
H (RA-V)	131.1[c]	152.5[c]	164.2[c]	165.3°)			20	30	40	50
							0/7	2/7	5/7	5/5
CH_3(RA-VII)	138.6[c]	156.7°)	164.2°)	173.6[b]		10	15	20	30	
						0/3	3/3	3/3	3/3	
CH2CH3	137.3[c]	165.4°)	162.2	Toxic	5	10				
					1/3	3/3				
$(CH_2)_2CH_3$	138.4[c]	146.0[a]	93.7	Toxic	5	10				
					1/3	3/3				
$CH(CH_3)_2$	142.2b)	175.1[c-e]	105.4	Toxic	5	10				
					3/3	3/3				
$(CH_2)_3CH_3$	133.0[c]	144.9[a]	Toxic	Toxic	5	10		20		
					0/3	3/3		3/3		
$(CH_2)_4CH_3$	122.2°)	142.7°)	165.4°)	Toxic	5	10		20	30	
					0/3	0/3		1/3	3/3	
$(CH_2)_5CH_3$	110.3[b]	137.3°)	153.5°)	173.0		10				
						0/3				
$(CH_2)_6CH_3$	115.8[c]	144.7°)	150.1°)	164.0[b]						
$(CH_2)_7CH_3$	136.1	146.8[c]	162.9[c]	152.2[b]						
$(CH_2)_8CH_3$	112.5[b]	141.5[b]	150.1[c]	155.4[b]						
$(CH_2)_9CH_3$	101.0	120.2[b]	132.7[c]	137.5[a]						
$(CH_2)_{10}CH_3$	115.4	108.7	121.2[b]	123.1[c]						
$(CH_2)_{11}CH_3$	93.0	101.0	105.8	112.5[a]						
$(CH_2)_{12}CH_3$	93.0	99.0	115.4	125.0°)						
$(CH_2)_{17}CH_3$	101.0	98.1	101.0	108.7						
	126.5	162.2	164.3[b]	Toxic						
	127.6	140.5[a]	149.2[c]	143.8						

Significantly different from control at

a) p<0.05

b) p<0.01

c) p<0.001, and from RA-V at

d) p<0.05, from RA-VII at

e)
p<0.05.
f)
Toxicity: number dead/number tested.

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Six-membered Rings with Two or More Heteroatoms and Fused Carbocyclic Derivatives

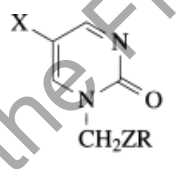
Kjell Undheim, Tore Benneche, in Comprehensive Heterocyclic Chemistry II, 1996

6.02.12.1.10 Antitumor agents

5-Fluorouracil has antineoplastic activity and is a valuable drug especially for the treatment of tumors of the colon or rectum, but it has a wider application in cancer chemotherapy.

Cytarabine, 4-amino-1-β-d-arabinofuranosylpyrimidin-2(1*H*)-one (cytosine arabinoside) is a valuable drug in cancer chemotherapy, as in the treatment of acute leukemias of childhood and adult granulocytic leukemia.

Certain 5-halo-2(1*H*)-pyrimidinones (**671**) will arrest the cell cycle of mouse and human cells grown in cultures. The arrest is in the relatively narrow metaphase region. Compounds have been found where the metaphase arrest is reversed when the active compound is removed, and the cells suffer no damage provided that the time of arrest is no longer than the cell cycling time. Cycling cells of all origin will be arrested in metaphase. With a rapid release of the block, parasynchronous resumption of the cell cycle leads to separation of the cells into groups because of kinetic differences between the different types of cells. The principle is thought to be applicable to achieve differential synchronization of cycling cells from normal and abnormal tissue in diseases caused by rapidly proliferating cells. Thus, sequential timed treatment with a phase-specific cytotoxic drug may be used to increase the kill of abnormal cells after pretreatment with a synchronizing agent 〈B-89MI 602-01, 91ACS177, 93EJM463〉.



(671)

X = F, Cl, Br, I
Z = O, S, NR, CO, CH=CH, C≡C
R = Ar, Alk, H

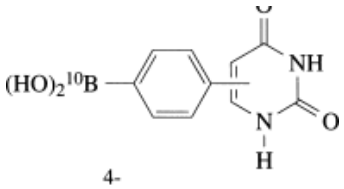
The 5-bromo and 5-chloro derivatives of 1-propargyl-2(1*H*)-pyrimidinones are inhibitors of the micotubule system in malignant cells. In rat glioma cells, arrest of mitosis was accompanied by repeated cycles of DNA synthesis, leading to different levels of polyploidization with formation of up to 16 and 32 ploid cells 〈86MI 602-04〉.

Synergistic cell inactivation effects were displayed when human NHIK 3025 cells cultivated *in vitro* were treated with 5-halo-2(1*H*)-pyrimidinones in combination with *cis*-diaminedichloroplatinum(II) (cisplatin) 〈88MI 602-02〉. *cis*-Diamineplatinum 1-methyluracil blue $[Pt_4(NH_3)_8(1\text{-MeU})_4]^{5+}$, where 1-MeU denotes 1-methyluracil, referred to as "platinum pyrimidine blues," belongs to a class of blue platinum complexes which are claimed to have a higher index of antitumor activity and lower nephrotoxicity than the anticancer drug *cis*-diaminedichloroplatinum(II). X-ray crystal structure data and magnetic and spectroscopic data are available 〈84JA6428〉.

The tetranuclear metal complex, $[(1,2\text{-diaminoethane})Pt(\text{uracilate-}N1,N3)]^{4+}$, can be considered a special heterocalixarene, a metal analogue of calix[4]arene which functions as hosts for small molecules or ions and possesses metal binding properties, either in the cavity or at the periphery. The bridging unit of the classical

calix[4]arene, usually a CH_2 group, is replaced by the (en)Pt(II) unit in the Pt-complex. This change, the replacement of the *p*-phenol by the 2,4-dioxopyrimidine and the positive charge introduced by the metal cations, leads to a number of differences as compared with the classical calix[4]arenes. Their preparation, x-ray crystal structure, and solution behavior have been described ⟨94JA616⟩.

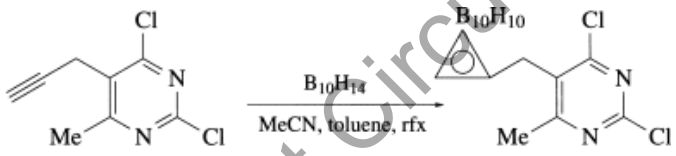
Boron-containing pyrimidines have been prepared for specific testing as agents for boron neutron capture therapy (BNCT). The diverse pathways by which pyrimidines and their nucleosides are utilized in the cell make these bioactive molecules a particularly attractive target for boronation in order to concentrate ^{10}B in actively replicating tissue. 5-(Dihydroxyboryl)uridine (DBDU) and -uracils (**672**) are available ⟨85JOC841, 89JOC4734⟩.



4-
5-

(672)

2,4-Dichloro-5-(1-*o*-carboranylmethyl)-6-methylpyrimidine (**674**) is said to be a potential synthon for the preparation of 5-(1-*o*-carboranylmethyl)-6-methylpyrimidines; chemoselective nucleophilic substitution of the chlorine atoms can be effected, and the cage can be selectively degraded for the preparation of more water-soluble *nido*-undecarborate derivatives. Preparation of the target molecule (**674**) is effected by the addition of decaborane to an appropriate alkyne (**673**) as shown in Equation (19) ⟨91JOC2391⟩.



(19)

(673) **(674)**

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Bryostatin 1

Cameron McIlwain, in xPharm: The Comprehensive Pharmacology Reference, 2008

Introduction

Bryostatin 1 is a macrocyclic lactone with antineoplastic activity. Bryostatin 1 binds to the cysteine rich domains of protein kinase C (PKC) resulting in its activation and translocation to the cell membrane. After phosphorylating specific protein substrates, PKC is ubiquitinated and targeted for proteolysis. Bryostatin 1 has been shown to reduce tumor cell proliferation, likely through the induction of tumor cell differentiation, and also causes tumor cell apoptosis. As the down-regulation of PKC may enhance cytotoxicity of other anti-cancer drugs, Bryostatin 1 acts synergistically with these agents (Sigma Product Information).

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Electrochemical Biosensors for DNA–Drug Interactions

S.C.B. de Oliveira, ... A.M. Oliveira-Brett, in Encyclopedia of Interfacial Chemistry, 2018

Adriamycin

ADM is an anthracycline antibiotic with numerous applications including antineoplastic activity by causing significant death of tumor cells. Its mode of action is not yet understood; however, it has been postulated that it intercalates mainly within CG–GC base pairs in the minor grove of dsDNA.[20]

The electrochemical behavior of ADM[20] has shown that different ADM groups can be oxidized and reduced. The 5,12-diquinone group irreversible reduction occurred at – 0.4 V and – 0.6 V, while the 6,11-dihidroquinone-functionality reversible oxidation occurred at + 0.5 V.

The in situ interaction between ADM and DNA, using a thick-layer dsDNA-electrochemical biosensor,[20] after applying a potential of – 0.60 V during 60 s, showed DNA oxidative damage. The reduced ADM radical produced at this applied potential was responsible for the DNA oxidative damage (**Fig. 7A**) detected by the occurrence of the biomarker 8-oxoG oxidation peak. A mechanism for DNA oxidative damage caused by ADM was proposed (**Fig. 7B**).

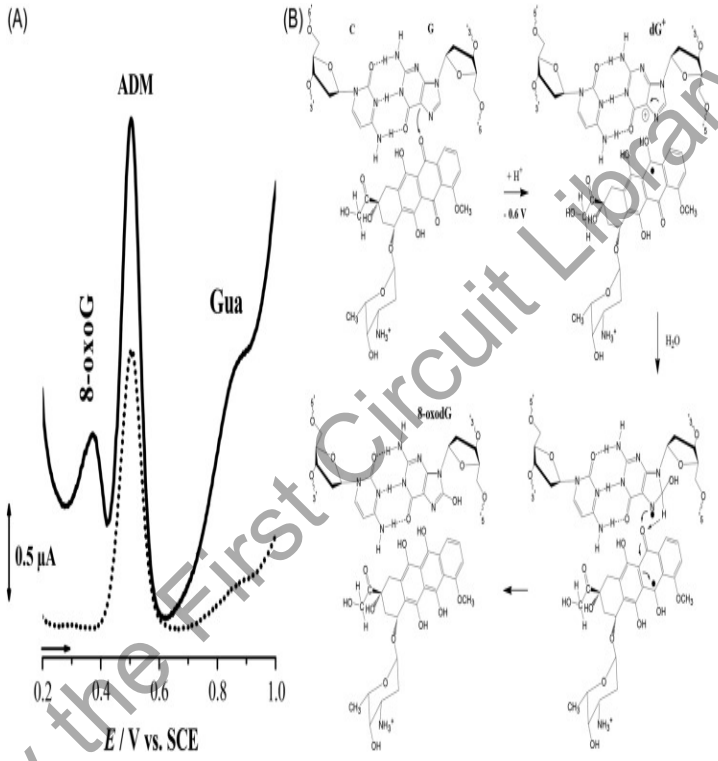

Fig. 7. (A) DP voltammograms, at a thick-layer dsDNA-electrochemical biosensor, in acetate buffer pH = 4.5, after incubation in a solution of 5 µM ADM, during 3 min: (•••) without applied potential, and (–) after applying a potential of – 0.6 V during 60 s; (B) Proposed mechanism of electrochemical *in situ* ADM oxidative damage to DNA.

[Adapted from Piedade, J. A. P.; Fernandes, I. R.; Oliveira-Brett, A. M. Electrochemical Sensing of DNA-Adriamycin Interactions. *Bioelectrochemistry* **2002**, *56*, 81–83, with permission.]

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Repurposing nonantibiotic drugs as antibacterials

Ritesh Thakare, ... Sidharth Chopra, in Drug Discovery Targeting Drug-Resistant Bacteria, 2020

8 Niclosamide

Niclosamide is a chlorinated salicylanilide possessing anthelmintic and potential antineoplastic activity. It is currently used against most tapeworm infections such

as intestinal nematodes, filarial nematodes, flukes, and tapeworms. Niclosamide has been approved for nearly 50 years for the treatment of such infections in humans [58]. Niclosamide has been identified as a potential anticancer agent by various high-throughput screening campaigns [59].

The antibacterial activity of niclosamide has been investigated against ESKAPE pathogens. It demonstrated potent activity against the Gram-positive bacteria such as *S. aureus* (0.125 μg/mL) and *E. faecium* (0.25 μg/mL), while it failed to exhibit the antibacterial activity against Gram-negative pathogen (MIC 64 μg/mL) [4]. Surprisingly, it has exhibited potent antibacterial activity against *Helicobacter pylori* (0.25 μg/mL) with immunomodulatory effect by decreasing secretion of IL-8 in a gastric cancer cell line after *H. pylori* infection [60]. The antibacterial activity of niclosamide was not limited to only the Gram-positive members of the ESKAPE pathogens, it also exhibited potent activity against *S. epidermidis* and *S. pyogenes* with an MIC of 0.125 μg/mL.

Further, it has demonstrated synergy with colistin against colistin-resistant strains of *A. baumannii* and *K. pneumoniae*. Niclosamide alone exhibited a range of MIC from 6.25 to 400 μM for colistin-susceptible and colistin-resistant *A. baumannii* strains and from 400 to >800 μM for *K. pneumoniae* strains. Niclosamide at 1–4 μM in a combination with colistin increased the activity of colistin significantly. In these bacteria, niclosamide increased the proportion of negative charges on their cell walls and thus was able to potentiate the activity of colistin against colistin-resistant *A. baumannii* and *K. pneumoniae* [61].

Intriguingly, niclosamide appeared to have no antibacterial activity against *P. aeruginosa*, but it has been observed to inhibit *P. aeruginosa* quorum sensing (QS) and thus inhibits biofilms [62]. In addition, with strong antibiofilm activity against Gram-positive bacteria, niclosamide has been evaluated as a versatile antimicrobial surface coating against device-associated, hospital-acquired bacterial infections [63]. Broad spectrum antibacterial activity in Gram-positive bacteria, those associated with hospital-acquired and device-associated infections, was assessed, and niclosamide-coated device was found to prevent and treat bacterial infections even at low concentration. Interestingly, no resistance was developed even after an exposure of *H. pylori* bacteria to niclosamide for 30 days.

The in vivo efficacy of niclosamide was investigated in *Galleria mellonella* model of *H. pylori* infection. Briefly, randomly selected *G. mellonella* larvae weighing 300–350 mg were infected with 10 μL *H. pylori* cells (OD600 = 0.3) in the last left proleg using a 10 μL Hamilton syringe. After 2-h post infection, compounds were administered at into the last right proleg and the larvae were incubated at 37°C and monitored afterward. They were considered dead if they lacked response to external stimuli. The niclosamide-treated group significantly rescued larvae with a survival rate up to ~70% compared to the no treatment group ($P < .0001$), while a clarithromycin administered group demonstrated ~80% survival over 5 day treatment [60].

The mechanism of action of niclosamide has been demonstrated to block glucose uptake, thus acting as an uncoupling agent for energy-generating oxidative phosphorylation in intestinal worms, starving the worms of ATP [64]. However, in bacteria, niclosamide acts through disruption of *H. pylori* proton motive force, and dissipation of proton is responsible for the anti-*H. pylori* activity [60].

Niclosamide is a safe drug because very little is absorbed from the gastrointestinal tract, and it is well tolerated in humans. Currently, for the treatment of *Taenia saginata* (beef tapeworm), *Diphyllobothrium latum* (fish tapeworm), and *Dipylidium caninum* (dog tapeworm) in adults, is given single oral dose of 2 g. For the treatment of *Hymenolepis nana* (dwarf tapeworm), the same oral dose is used for 7 days [58] with minimal side effects. Taken together, potential of niclosamide as antibacterial therapy or as a device coating to prevent biofilm formation and clear existing infections warrants its repurposing as antibacterial.

Perifosine

Vladimir Beljanski, in xPharm: The Comprehensive Pharmacology Reference, 2007

Introduction

Perifosine is an orally bioavailable alkyl-phosphocholine drug with antineoplastic activity. Perifosine is designed to target cellular membranes, and its presence influences membrane permeability, lipid composition, phospholipid metabolism, and mitogenic signal transduction, resulting in cell differentiation and inhibition of cell growth in vitro and in vivo in several human tumor model systems. This agent also inhibits the MAPK pathway and modulates the balance between the MAPK and pro-apoptotic stress-activated protein kinase (SAPK/JNK) pathways, and through its anti-Akt action, may enhance the effects of other treatment agents by promoting apoptosis and interfering with cell growth signals. Vink et al (2005), Agresta et al (2003).

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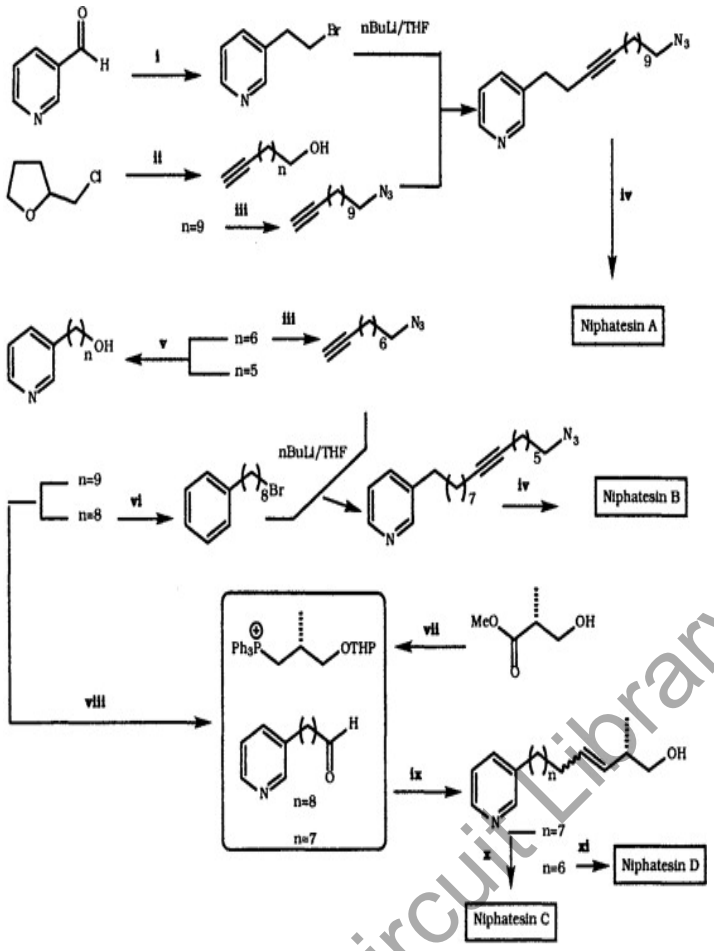
Bioactive Natural Products (Part E)

Jaime Rodriguez, in Studies in Natural Products Chemistry, 2000

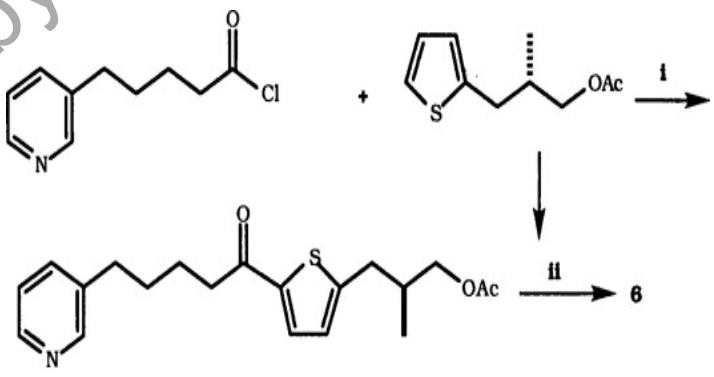
Niphatesines A–H (4–11).

Niphatesines A–D (**4–7**) showed antineoplastic activity and they were found in another Niphates species from the sea around Okinawa [123]. The total synthesis of **4–7** has been approached by two different research groups. A first regio/enantioselective synthesis was achieved (see Scheme 1) by making use of the extremely versatile Pd(0) chemistry, which assisted the 3-pyridine alkylation in the key step. At the same time the absolute configuration of niphatesin C (6) and D (7) was established [24]. A different, thiophene-based approach was used to complete the total synthesis of both enantiomers of niphatesin C (see Scheme 2). In this case the absolute configuration was established on the basis of the comparison of the sense of optical rotation with that of the natural product [25]. Niphatesin A (**4**) was also synthesized in a simple manner via an alkyne derivative (see Scheme 6).



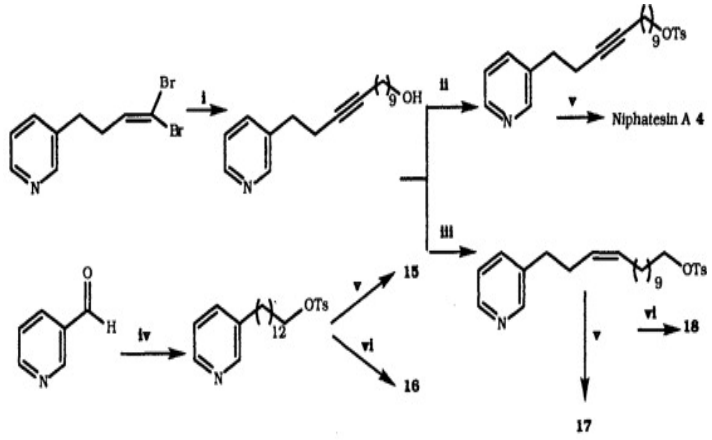
i. 1) $CH_3P^+Ph_3Br^\ominus$, $NaNH_2$. 2)BH_3/THF, NaOAc, H_2O_2
ii. 1)$LiNH_2$/liq. NH_3, CH_3-$(CH_2)_n$Br; 2) $NaNH_2$, H_2N-$(CH_2)_3$-NH_2, Δ
iii 1) $NaNH_3$, DEAD, PPh_3, PhH
iv, 1) $LiAlH_4$, THF, 0°C
v, 1) Pd-$CaCO_3$/H_2, MeOH; 2) $Pd(OAc)_2$, PPh_3, $NaHCO_3$, DMF, Δ; 3) Pd/C, H_2, MeOH
vi. 1) 48% aq. HBr
vii. 1) DHP, TsOH; 2) $LiAlH_4$, THF; 3) MsCl, CH_2Cl_2; 4) LiBr, acetone; 5) PPh_3, CH_3CN
viii. 1) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2
ix. 1) nBuLi, THF; 2) HCl, MeOH
x. 1) NaN_3, DEAD, PPh_3, PhH; 2) Pd/C, H_2, MeOH
xi. 1) TsCl, CH_2Cl_2; 2) NaCN, DMF, Δ; 3) Pd/C, H_2, MeOH

Scheme 1. Total synthesis of niphatesines A-D (**4**–**7**).



i. 1) $SnCl_4$, CH_2Cl_2
ii. 1) KOH, NH_2-NH_2, diethylene glycol; 2) Ni Raney, H_2, THF; 3) MsCl, pyridine; 4) NaN_3, DMF; 5) Pd/C, H_2, EtOH

Scheme 2. Total synthesis of the alkaloid niphatesine **C** (**6**).

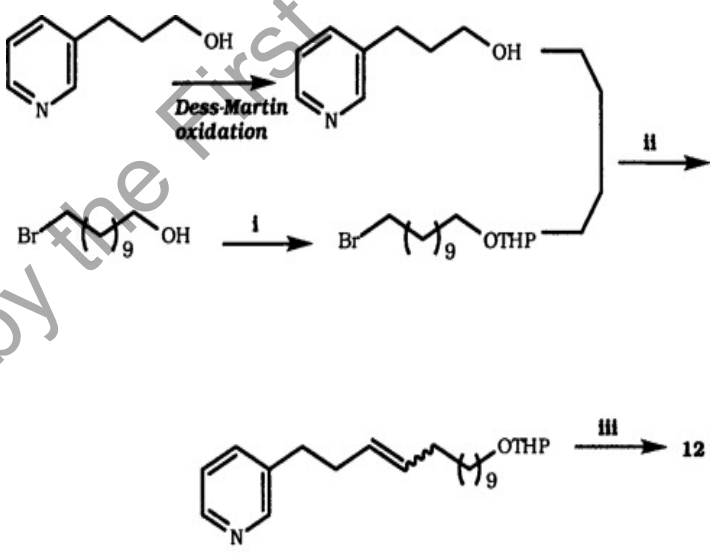


i. 1) nBuLi (2eq.), THF; 2) nBuLi, THF, $Br(CH_2)_{10}OTHP$, HMPT
ii. 1) TsCl, pyridine
iii. 1) H_2, Lindlar, cyclohexane; 2) TsCl, pyridine
iv. 1) $Br(CH_2)_{12}OBn$, Mg, Br_2CH_2, Et_2O, THF; 2) Swern-Oxidation; 3) NH_2-NH_2, EtOH, diethylenglycol KOH; 4) CITs, pyridine
v. 1) NH_3, EtOH
vii. 1) $MeNH_2$, EtOH

Scheme 6. Total synthesis of Niphatesin A (**4**) and Theonelladines A-D (**15–18**).

Niphatesines E–H (**8–11**): Oxime, methyl ether or methoxyamine functionalities are present in the niphatesines E (**8**), F (**9**), G (**10**) and H (**11**), which were isolated off the Kerama Islands (Okinawan sea, Japan) [26]. **8–11** showed mild cytotoxic and antimicrobial activities.

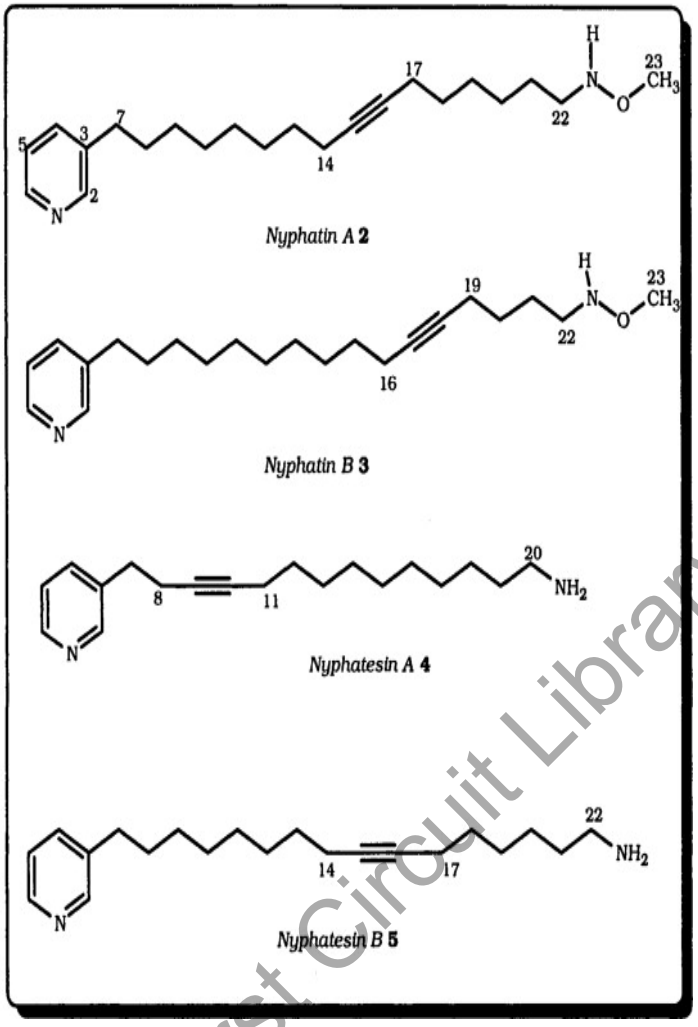
Untenines A–C (**12** and **13**): Three novel nitroalkyl pyridine alkaloids [27] with anti-microfouling activity were first isolated from *Callyspongia* sp. Their structures were elucidated by NMR and HREIMS. The total synthesis of untenine A (**12**) was completed by Dess–Martin oxidation of 3-piperidinepropanol and using a Wittig reaction as a key step (see Scheme 3).

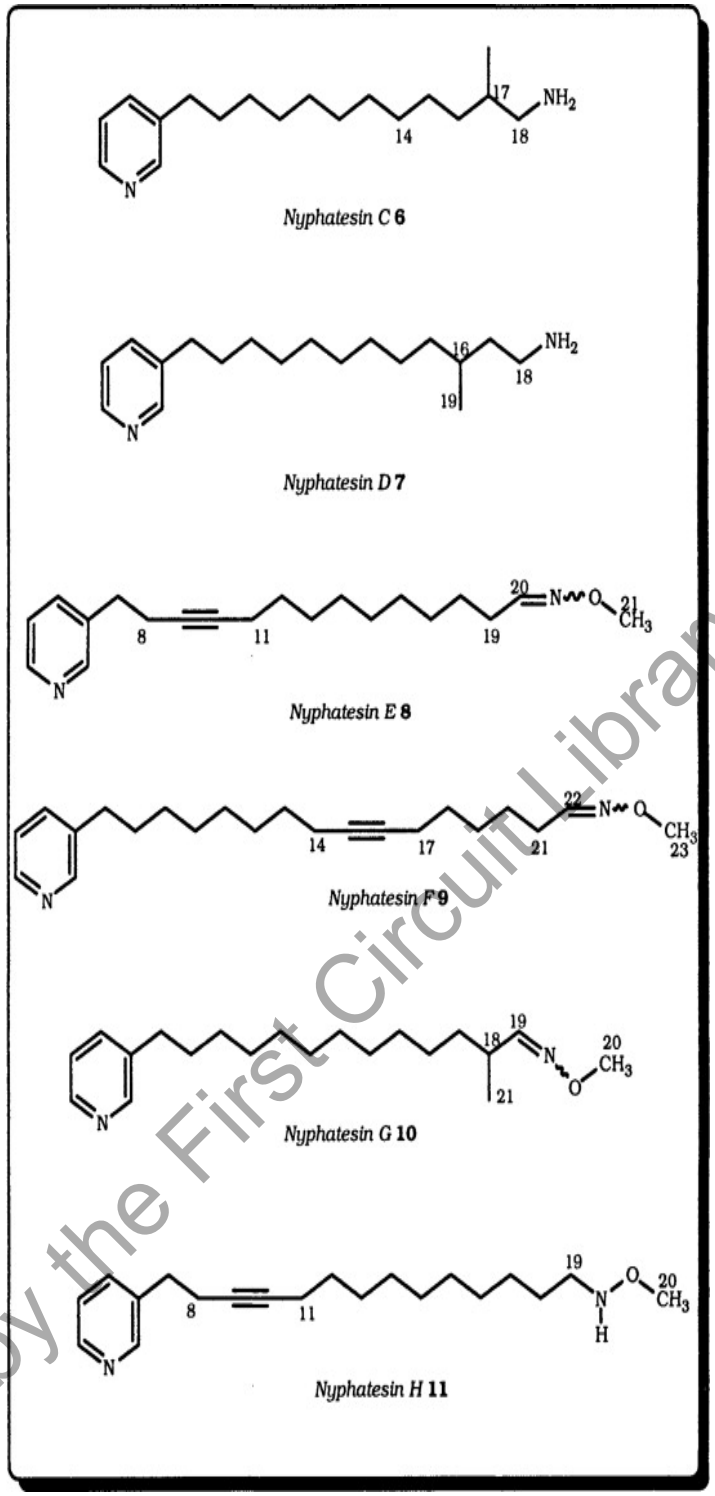


i. 1) DHP, TsOH, CH_2Cl_2; 2) Ph_3P, MeCN
ii. 1) NaH, DMSO
iii. 1) AcOH, THF, H_2O; 2) CBr_4, Ph_3P, CH_2Cl_2; 3) $AgNO_2$, ether

Scheme 3. Total synthesis of untenine A.

Monomers of 3-alkylpyridines from marine sponges





Lycopene

Montaña Cámara, ... Jorge O. Caceres, in Studies in Natural Products Chemistry, 2013

Antineoplastic Activity

According to Clinton [29], much of lycopene's antineoplastic activity may be attributed to its antioxidant properties. However, other mechanisms underlying the inhibitory effects of lycopene on carcinogenesis have been described, such as upregulation of detoxification systems, interference with cell proliferation,

induction of gap junctional communication (GJC), inhibition of cell cycle progression, and modulation of signal transduction pathways [80].

The antineoplastic activity of lycopene may be due to its inhibition of DNA synthesis [33]. Lycopene strongly inhibited proliferation of endometrial (Ishikawa), mammary (MCF-7), and lung (NCI-H226) human cancer cells with the half-maximal inhibitory concentration of 1–2 μM; lycopene also suppressed insulin-like growth factor-I-stimulated growth. Inhibition of cell proliferation by lycopene may involve a modulation of protein kinase C (PKC) activity, which is important in the signal transduction pathway leading to cell proliferation [81]. Thus, inhibition of proliferation might also be linked to lycopene's antioxidant effect.

Modulation of intercellular communication, which has been demonstrated in cell cultures, may be another mechanism for the antiproliferative effect of lycopene. The scientific findings show that lycopene differentially modulates gap-junctional intercellular communication (GJIC) depending on the dose, with beneficial effects on cell communication [82,83]. Lycopene may stimulate GJC through stabilization of connexin43 mRNA [84].

Another postulated mechanism for the antiproliferative effect of lycopene is inducing differentiation of cancer cells. This induction of differentiation has been observed in leukemic cell cultures exposed to a combination of both lycopene and 1,25 dihydroxyvitamin D3 [85].

In breast and endometrial cancer, lycopene's mechanism of action is based on the inhibition of cell cycle progression associated with reduction in cyclin D levels and retention of p27Kip1 in the cyclin E binds to G1 phase—cyclin-dependent kinase 2 (E-cdk2) complexes. In prostate cancer, different mechanisms are proposed for the inhibition of cancerous cell proliferation at the G0–G1 cell cycle transition and protection of DNA [86].

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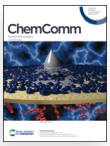

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