

# MODELING AND APPROACHES TOWARD THE SYNTHESIS OF BIOACTIVE MARINE MACROLIDES ALKALOIDS (NETAMINES)

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Alkaloids have been grouped to be one of the widest classes of natural products. It is synthesized practically by all phyla, both marine and terrestrial organisms [1]. Toxicologists, pharmacologists and pharmaceutical companies have used and will continue to use alkaloids as biological tools and/or as lead compounds for development of new drugs [1]. The extraordinary variety of alkaloid structures and its biological properties made chemists interested to study them further, be it for structure determination or biosynthetic studies.

Polycyclic guanidine alkaloids are a unique class of sponge-derived metabolites showing broad range of biological activities [2]. Recent interest in guanidine alkaloids [3] renders molecules containing guanidine moiety important targets. For example, the alkaloid ptilomycalin A [4], isolated from the Caribbean sponge *Ptilocaulus spiculifer* and from a Red Sea sponge of *Hemimycale* sp, have been reported to exhibit cytotoxic, antiviral and antifungal activities [5], [6]. The guanidine functional group is reported to be a key feature in many biologically active compounds [7], due to hydrogen bond mediated interaction with phosphate and carboxylate containing molecules [8].

Netamines is a class of polycyclic guanidine extracted from Poeciloscleridae sponge *Biemna laboutei*, a marine sponge. Specifically, netamine is a tricyclic guanidine alkaloid and in addition to being cytotoxic, it has been reported to possess biological activities such as HIV gp120-human CD4-binding inhibition, p56<sup>lck</sup>-CD4 dissociation induction, Ca<sup>2+</sup> channel blocker activities, cytotoxicity, and antifungal and antimicrobial activities (10). For example, netamine C and D were reported to be cytotoxic against three tumor cells with GI<sub>50</sub> values in the micromolar range [10]. However, thus far, in spite of the various activities, particularly against cancer cells, there have not been not much report on how or where netamines act.

Our work aims to understand the mechanism of action of netamines and, subsequently design a netamine-based compound that could potentially be a lead as anti-cancer agent. Our approach

began with *in silico* docking studies. Information from these studies will then be used to design and synthesize a netamine derivative for validation of the model.

The ligand was built *in-silico* based in figure 1 using Hyperchem Professional 8.0 software. Geometry optimization is performed using the function of Steepest Descent followed by Polak-Ribiere at the RMS Gradient of 0.001 kcal/mol (Å/mol) until the molecule is fully converged. Cancer cells receptors (macromolecule) were obtained from the Protein Databank (PDB) comprising the androgen, estrogen, both alpha and beta, and progesterone. Autodock 4.0 (Linux) was used for docking of ligands to the receptors and dlq files were generated for data analyses of interaction between the ligand and the macromolecule. All data collected (blind docking and specific docking) were analyzed using software such as Accelrys Viewerlite, Accelrys Discovery Studio 2.5 and Ligplot.

Docking studies were carried out between Netamines A-G (Figure 1) with various cancer cell receptors and summarized in Table 1. Results seemed to indicate the best binding for netamines A and D to various receptors (Table 2), in particular, netamine D to the receptor 1E3G.

**Table 1.** Summary of binding between various netamines and receptors

<b>Receptor</b>	<b>Ligand</b>
1A52.pdb	Netamine A, B, D
1E3G.pdb	Netamine A, B, <b>D</b>
1QKM.pdb	Netamine A, C, D
1SQN.pdb	Netamine A, B, D
2AM9.pdb	Netamine B, D
3ERD.pdb	Netamine B, D

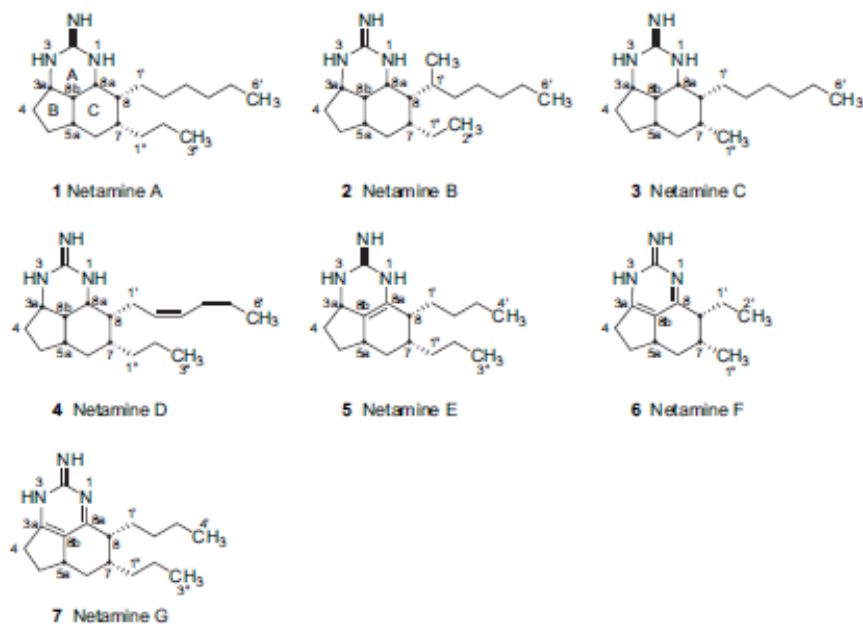


Figure 1: Structures of netamines A-G

**Table 1.** Binding energies between the various ligands and cancer receptors (kcal/mol)

		LIGANDS						
		Netamine A	Netamine B	Netamine C	Netamine D	Netamine E	Netamine F	Netamine G
TORSRECEP	1A52	-7.94	-7.99	-7.65	-7.98	-7.32	-6.28	-6.76
		-7.73	-7.46	-7.32	-7.79	-6.90	-6.08	-6.40
		-7.42	-7.33	-7.32	-7.49	-6.72	-	-6.35
	1E3G	-8.93	-8.89	-8.28	-9.08	-7.99	-7.23	-7.72
		-8.72	-8.68	-8.27	-8.78	-7.96	-	-7.45
		-8.45	-8.46	-8.25	-8.73	-7.87	-	-7.26
1QKM	-8.31	-8.04	-8.63	-8.39	-7.50	-6.40	-7.12	
	-8.16	-7.86	-	-8.37	-7.27	-6.34	-7.09	
	-7.70	-	-	-7.84	-	-	-6.99	
1SQN	-8.32	-8.49	-7.81	-8.43	-7.47	-6.65	-7.12	
	-8.26	-7.93	-7.76	-8.40	-7.47	-	-6.97	
	-7.96	-	-7.61	-8.23	-7.15	-	-6.86	
2AM9	-7.84	-8.08	-7.62	-8.09	-7.56	-6.47	-6.98	
	-7.73	-7.96	-7.59	-7.81	-7.32	-	-6.71	
	-7.52	-7.72	-7.42	-7.60	-7.16	-	-6.60	
3ERD	-7.99	-8.26	-7.59	-8.02	-7.51	-6.19	-6.90	
	-7.47	-7.62	-7.38	-7.68	-7.38	-5.79	-6.72	
	-7.46	-7.46	-7.29	-7.56	-	-	-6.58	

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