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Review article

# Dictyoceratidan poisons: Defined mark on microtubule-tubulin dynamics

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ABSTRACT

Tubulin/microtubule assembly and disassembly is characterized as one of the chief processes during cell growth and division. Hence drugs those perturb these process are considered to be effective in killing fast multiplying cancer cells. There is a collection of natural compounds which disturb microtubule/tubulin dis/assemblage and there have been a lot of efforts concerted in the marine realm too, to surveying such killer molecules. Close to half the natural compounds shooting out from marine invertebrates are generally with no traceable definite mechanisms of action though may be tough *anti*-cancerous hits at nanogram levels, hence fatefully those discoveries conclude therein without a capacity of translation from laboratory to pharmacy. Astoundingly at least 50% of natural compounds which have definite mechanisms of action causing disorders in tubulin/microtubule kinetics have an isolation history from sponges belonging to the Phylum: Porifera. Poriferans have always been a wonder worker to treat cancers with a choice of, yet precise targets on cancerous tissues. There is a specific order: Dictyoceratida within this Phylum which has contributed to yielding at least 50% of effective compounds possessing this unique mechanism of action mentioned above. However, not much notice is driven to Dictyoceratidans alongside the order: Demospongiae thus dictating the need to know its select microtubule/tubulin irritants since the unearthing of avarol in the year 1974 till date. Hence this review selectively pinpoints all the compounds, noteworthy derivatives and analogs stemming from order: Dictyoceratida focusing on the past, present and future.



**Contents**



## 1. Introduction

One of the prime group of organisms that accounted for huge entries in the natural products libraries would be invertebrates, precisely from marine environs [1, 2]. Umpteen numbers of bioactive natural products

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have been identified and discussed from marine invertebrates in the past decades with special prominence to Phylum: Porifera [3, 4, 5, 6]. These invertebrates participate in varied interactions within themselves and as well with other groups majorly by chemically-intervened processes. This feature had directed focused researches to target compounds of therapeutic significance, precisely against cancer in recent times [7, 8, 9]. Poriferans have been in strong nominations for more than four decades as target groups for anticancer drugs. Whilst a large number of these sponge-derived metabolites are tagged as ideal candidates for the treatment of deadly diseases, those that target tubulin/microtubule dynamics are only close to 11 in numbers.

Microtubule-tubulin dynamics is a major player for very many processes occurring in the cells, including its maintenance and internal vesicular movement and cell division. This dynamic nature is considered as a plump target as anticancer drugs since cancer cells are active participants of mitosis and cell division [10, 11, 12]. Anticancer therapists believe that any distraction thereof in microtubule-tubulin kinetics may lead to blockades in the cell cycle progression in a vast majority of cells that are in transition from prometaphase/metaphase to anaphase. There are many drug binding sites on microtubule/tubulin, however three among them are opinioned as well established ones, a) vinca, b) taxane and c) colchicine binding sites. The vinca domain is present near the interchangeable GTP binding site of tubulin [plus end interface] [13, 14], the taxane domain dwells in a deep hydrophobic compartment sideward between the compact protofilaments, within the lumen of the microtubule [at the minus end] [15, 16, 17]. However at the intra-dimer boundary between tubulin and tubulin is found the colchicine site [18, 19].

Dictyoceratida, one of the seven orders of the Class: Demospongiae which are so-called "keratose sponges", lack spicules. Their skeletons feature anastomosing spongin fibres and specimens coming under this category are resilient, easily squeezable but tough to tear because of collagen fibres as the major content. Biochemically this order is characterized by a lesser sterol content and an array of terpenes within the lipid fractions. Past four decades (1970–2010) have been a golden era for the discovery of innovative microtubule/tubulin-disrupting anticancer agents from the order: Dictyoceratida. A review on microtubule targets from Poriferans indicates that 4 hits out of 8 come from Dictyoceratidans [9]. The Marine Natural Products Library has entries of the most efficient natural compounds and their derivatives from this order: Avarols (1970–1980), Laulimalides (1980–1990), Spongistatins, Dictyostatins, Arenastatins, Zampanolide (1990–2000) and Dactylolide (2000 — 2010) (Fig. 1). Much of the active compounds accounted by Poriferans stems by and large from Dictyoceratidans, though this order has only 5 families unlike others (Haplosclerida and Poecilosclerida) with more than 10 families. Also the anticipation generated by Halichondrians could not be any way in match with Dictyocertidans which could be possibly due to less-than-nominal literature appraisals. The *hitherto* reported new mechanisms of action for these fresh compounds and an abrupt discontinuance in research clearly point toward the requirement of more appraisals. Hence it was felt essential to assess the important tubulin/microtubule compounds from this chemo-prolific order. Therefore an overall picture of natural compounds and noteworthy analogs from this group are recorded herewith. This paper reviews 1) significant microtubule-tubulin disturbing compounds from Order: Dictyoceratida with reference to history of isolation; 2) their select derivatives and analogs with highlights on significant synthesis efforts and 3) current statuses in markets/clinical trials.

## 2. Dictyoceratidan chemotypes disturbing microtubule-tubulin kinetics

### *2.1. Avarols [microtubule depolymerizer]*

**Family**: Dysideidae

**Candidate organism**: *Dysidea avara*

The first evidence of a natural compound sourced from demospongians against cancer cells by inhibiting tubulin-microtubule assemblage is a sesquiterpenoid hydroquinone, avarol. This natural substance was first extracted in 1974 from a dictyocertidan sponge, *Dysidea*

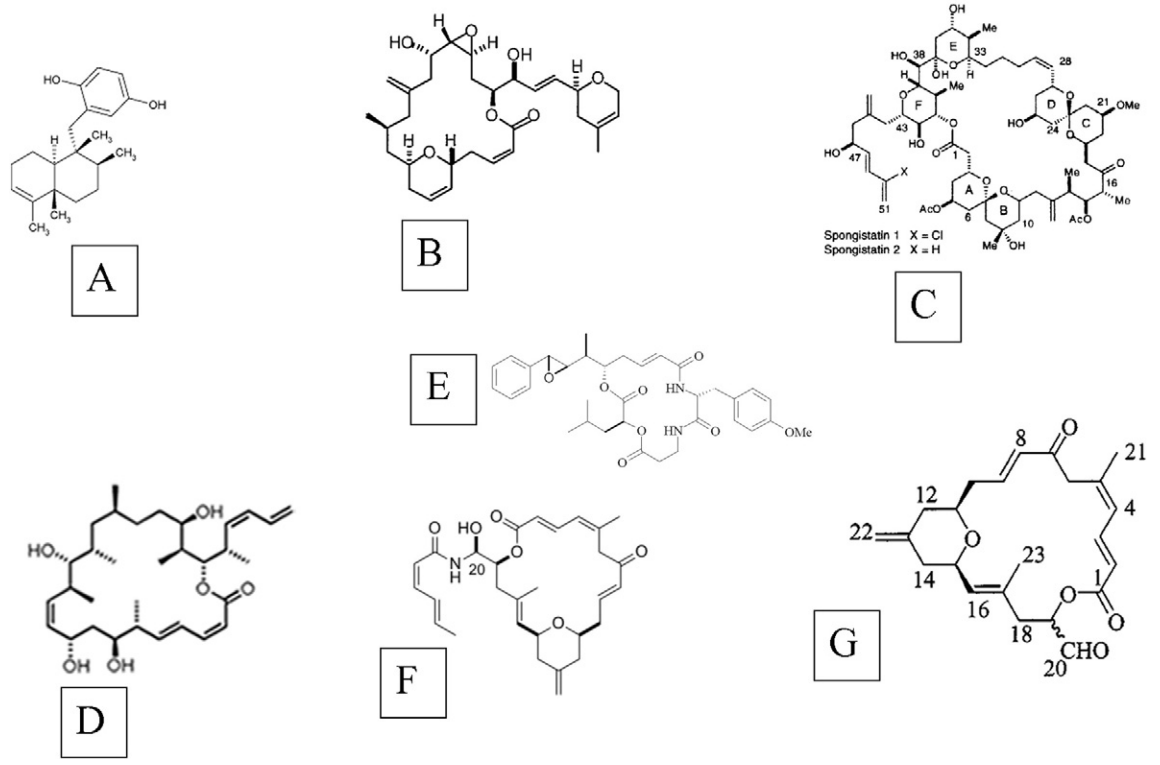


**Fig. 1.** Tubulin/microtubule disturbing chemotypes from Dictyoceratidans