Comparative Effects of Aplysiatoxin, Debromoaplysiatoxin, and Teleocidin on Receptor Binding and Phospholipid Metabolism

Ann D. Horowitz, Hirota Fujiki, I. Bernard Weinstein, Alan Jeffrey, Ester Okin, Richard E. Moore, and Takashi Sugimura

Division of Environmental Science and Cancer Center/Institute of Cancer Research, Columbia University, College of Physicians and Surgeons, New York, New York, 10032 [A. D. H., I. B. W., A. J., E. O.]; National Cancer Center Research Institute, Tsukiji 5-1-1, Chuo-Ku, Tokyo 104, Japan [H. F., T. S.]; and Department of Chemistry, University of Hawaii, Honolulu, Hawaii 96822 [R. E. M.]

ABSTRACT

We have compared the activities of apleisiatoxin and debromoaplysiatoxin, two polyacetate marine algae toxins, with teleocidin, a tumor-promoting indole alkaloid from Streptomyces, with respect to inhibition of specific binding of epidermal growth factor, and phorbol-12,13-dibutyrate to their respective receptors and ability to stimulate the release of radioactivity from cells prelabeled with choline or arachidonic acid. Although these compounds have chemical structures that are quite different from the phorbol esters, both apleisiatoxin and teleocidin are essentially equipotent with the potent tumor promoter 12-O-tetradecanoylphorbol-13-acetate in all four assays. The fact that apleisiatoxin and teleocidin inhibit phorbol-12,13-dibutyrate-receptor binding suggests that their biological activities are mediated by binding to the same receptors utilized by the phorbol esters. Debromoaplysiatoxin, a debrominated form of apleisiatoxin, is about 10-fold weaker than apleisiatoxin in inhibiting epidermal growth factor and phorbol-12,13-dibutyrate-receptor binding, but is equipotent with apleisiatoxin in stimulating the release of lipid metabolites from the prelabeled cells. The results are discussed in terms of possible heterogeneity of cellular receptors for this group of compounds.

INTRODUCTION

Until recently, the phorbol esters such as TPA and structurally related plant diterpene esters were the only class of skin tumor promoters capable of acting at nanomolar concentrations. In addition, these compounds can exert highly pleiotropic effects on growth and differentiation, and on membrane structure and functions when added to cell culture systems at nanomolar concentrations (for reviews, see Refs. 20, 48, and 60). In contrast, other types of skin tumor-promoting agents, such as phenols, fatty acids, and detergents, require at least micromolar concentrations. Generally, the phorbol esters are derived from the Euphorbia plant species, and have a tetracyclic diterpene ring system (16, 58). The phorbol esters are equipotent with TPA as a tumor promoter on mouse skin (11, 50–54) and Hirakawa et al. (17) also showed that dihydroteleocidin B markedly enhanced malignant cell transformation induced by 3-methylcholanthrene or UV radiation. Dihydroteleocidin B and the related indole alkaloids teleocidin, isolated from Streptomyces (55), and lyngbyatoxin A, isolated from marine blue-green alga (6), have also been shown to share with TPA many effects in cell culture systems, also acting at nanomolar concentrations and following time courses similar to those seen with TPA (9–11). These effects include induction of ornithine decarboxylase (10, 11); stimulation of arachidonic acid release, prostaglandin production, and choline turnover (44, 57); formation of superoxide anions (O₂⁻) and hydrogen peroxide (56); induction of Epstein-Barr virus expression and enhancement of Epstein-Barr virus-induced transformation (23, 61); induction of terminal differentiation (42) and adhesion (10, 11) of HL-60 cells; aggregation of human lymphoblastoid cells (22); induction of terminal differentiation of Friend erythroleukemia cells (10, 11); stimulation of 2-deoxyglucose transport (57); enhancement of transformation by adenovirus; enhanced cloning efficiency of adenovirus-transformed cells; inhibition of melanogenesis in B16 cells and inhibition of myogenesis in human myoblast cultures (9); and inhibition of binding of [¹²⁵I]EGF to its membrane receptors in a rat embryo cell line (57). In addition, teleocidin and dihydroteleocidin B inhibit the specific binding of the phorbol ester [³²P]PDBU to membrane-associated cellular receptors, at a potency similar to that of TPA (18, 47, 57). These findings are highly significant, since they provide evidence that these indole alkaloids represent a new class of potent tumor promoters that have a structure quite different from that of the phorbol esters, but which appear to bind to the same receptors and thus produce similar biological effects.

The phorbol esters are derived from the Euphorbia plant species, and have a tetracyclic diterpene ring system (16, 58). The potency of the phorbol esters depends in part on the hydrophobicity of the ester functions attached to this phorbol nucleus. Teleocidin has an indole ring and a 9-membered lactam ring (Chart 1). It is derived from Streptomyces mediocidicus (55). When extracted from Streptomyces, the material referred to as teleocidin is a mixture of teleocidin A and teleocidin B. Teleocidin B has a fourth closed ring system, whereas in teleocidin A the corresponding region contains an aliphatic side chain (Chart 1). Teleocidin A has the same 3-ringed structure as lyngbyatoxin A, which is derived from a marine blue-green alga, Lyngbya majuscula (8). More recently, a structurally distinct class of toxins

---

1 This work was supported in part by Grants-in-aid for Cancer Research from the Ministry of Education, Science and Culture of Japan, the Princess Takamatsu Cancer Research Fund, the United States-Japan Cooperative Cancer Research Program, and a research fellowship from the Dupont Company.

2 Recipient of National Cancer Institute Grant CA 26056. To whom requests for reprints should be addressed.

3 Recipient of National Cancer Institute Grant CA 12632.

4 The abbreviations used are: TPA, 12-O-tetradecanoylphorbol-13-acetate; EGF, epidermal growth factor; PDBU, phorbol-12,13-dibutyrate; DMEM, Dulbecco’s modified Eagle’s medium; PBS, phosphate-buffered saline; ED₅₀, dose producing 50% of maximal effect.

Received June 9, 1982; accepted December 10, 1982.
referred to as "polyacetates" (aplysia toxin and debromoaplysia toxin) (Chart 1) has become of interest. These compounds have been extracted from another variety of L. majuscula, and were first found in the digestive tract of the sea hare Stylocelis longicauda (28, 29, 41). Recently, it was found that these compounds represent a third class of tumor promoters in the 2-stage mouse skin carcinogenesis system (14), and that aplysia toxin and debromoaplysia toxin share a number of other biological effects with the phorbol ester and indole alkaloid tumor promoters. These include induction of irritancy and ornithine decarboxylase in mouse skin, induction of adhesion and phagocytosis by HL-60 cells, aggregation of NL-3 cells, and inhibition of differentiation of Friend erythroleukemia cells (14). An important aspect of the latter studies is the relative potencies of aplysia toxin and debromoaplysia toxin. With respect to induction of irritancy and ornithine decarboxylase, aplysia toxin and debromoaplysia toxin are equipotent; however, in the other 4 assays, debromoaplysia toxin is 50-100-fold less potent than aplysia toxin (11, 14, 50-54). In all of the above-mentioned assays, aplysia toxin is approximately as potent as TPA and teleocidin.

We were interested in studying these compounds further by systematically examining the effects of teleocidin, debromoaplysia toxin, and aplysia toxin with respect to membrane effects in cell culture systems. In particular, we wished to determine whether the polyacetates, like the indole alkaloids, might act by binding to the same receptors as the phorbol esters. In this study we report the effects of teleocidin, aplysia toxin, and debromoaplysia toxin on inhibition of binding of [3H]PDBU and [125I]EGF to their respective receptors, and on stimulation of the release of radioactivity from cells prelabeled with [3H]arachidonic acid or [3H]choline. We have conducted these assays in both the murine C3H 10T½ cell line and in CREF cells, a cell line derived from rat embryo fibroblasts (8).

MATERIALS AND METHODS

Materials. [3H]PDBU (6.4 Ci/mmol) from Life Systems Co. (Woburn, Mass.) was used in the intact cell assays. [125I]EGF (receptor grade, 179 μCi/μg) was from Collaborative Research (Waltham, Mass.). [methyl-3H]Choline (84 Ci/mmol) and [3H]arachidonic acid (120 Ci/mmol) were from Amersham Corp. (Arlington Heights, Ill.). C3H10T½ mouse embryo cells were used between Passages 8 and 15. CREF N cells are a line of rat embryo cells isolated and characterized by Fisher et al. (8). Both cell types were maintained in DMEM (Grand Island Biological Co., Grand Island, N. Y.) plus 10% calf serum (Flow Laboratories, McLean, Va.). Teleocidin, aplysia toxin, and debromoaplysia toxin were obtained as previously described (10, 11, 14). The teleocidin used was a mixture containing about 93% teleocidin A and 7% teleocidin B (11).

PDBU-binding Assay. The assay for specific binding of [3H]PDBU to monolayer cultures was conducted as previously described (18, 19). Cells were grown on 3.5-cm-diameter tissue culture dishes (Nunc, Roskilde, Denmark), and cultures were assayed for receptors when subconfluent. The monolayer was washed once with PBS and 1 ml of assay buffer (2 volumes DMEM, 1 volume PBS, plus bovine serum albumin at 1 mg/ml) was added. The cell monolayer was then incubated for 30 min at 37°C. [3H]PDBU and test compounds were added, and the cell monolayer was incubated at 37°C for 30 min. The monolayer was then washed rapidly 3 times with ice-cold assay buffer and solubilized by treatment for 2 hr at 37°C with solubilizing solution (0.8% Triton X-100, 0.2% EDTA, and 0.25% trypsin in PBS). The plates were washed 2 times with 1% sodium dodecyl sulfate. The solubilizing solution and washes were pooled and assayed for radioactivity in 15 ml of Hydrofluor (National Diagnostics). Nonspecific binding was that observed in the presence of 50 μM unlabeled PDBU. This value was subtracted from the total binding to obtain specific binding. All data are expressed as specific binding and represent the means of duplicate determinations. All experiments were repeated at least twice. Cell numbers were determined by counting in a Coulter Counter (Coulter Electronics, Inc., Hialeah, Fla.). For cell counts, the monolayers were washed 2 times with PBS and trypsinized with 0.25% trypsin in 0.02% EDTA in PBS. An aliquot was diluted in PBS or Hemastat isotonic diluent (Fisher Chemical Co., Springfield, N. J.) and counted in the Coulter Counter.

EGF-binding Assay. This assay was conducted in essentially the same manner as the PDBU-binding assay used with intact cells, except that the 30-min preincubation at 37°C was omitted. The assay system contained 0.7 ng [125I]EGF (rather than [3H]PDBU) per ml, and binding was allowed to occur for 50 min at 37°C. Nonspecific binding was that observed in the presence of 100 ng unlabeled EGF per ml, and was subtracted from the total bound radioactivity to obtain the specific binding.

Measurement of Release of Lipid Metabolites. The measurement of release of radioactivity from cells prelabeled with [3H]choline was conducted as described by Mufson et al. (39). Cells were plated at 1.5 × 10⁵ cells/50-mm plate in DMEM plus 10% calf serum. Twenty-four hr after plating 1 μCi of [3H]choline per ml was added to each plate. Twenty-four hr later the plates were washed 3 times with DMEM without serum. After the final wash, the compounds to be tested were added in 2.0 ml of DMEM, the plates were incubated at 37°C for 60 min, and the media was collected and centrifuged to eliminate cells or debris. Aliquots of the media (0.5 ml) were counted to obtain total [3H]choline metabolites released.

Studies with [3H]arachidonic acid were also conducted as previously described (38). Cells were plated at 1.5 × 10⁵ cells/50-mm plate in DMEM plus 10% calf serum. Twenty-four hr later, each plate received 5 μCi of [3H]arachidonic acid. After a 24-hr incubation period, the cultures were washed 3 times with DMEM without serum. After the final wash, the compounds to be tested were added in 2.0 ml of DMEM, and the cultures were incubated at 37°C for 3 hr. Aliquots of the media (0.5 ml) were collected and counted to obtain the total [3H]arachidonic acid metabolites released.

Previous studies (38, 39, 44) have provided evidence that the above assays measure the release of [3H]choline and [3H]arachidonic acid and
their metabolites from prelabeled cellular phospholipids, although the precise enzymology has not been elucidated (39).

RESULTS

Inhibition of Specific Binding of [3H]PDBU. Previous studies have shown that, in general, the ability of phorbol esters and closely related plant diterpenes to inhibit [3H]PDBU binding to membrane-associated receptors correlates well with tumor-promoting activity (7, 19-21, 46, 47). We have also shown that the indole alkaloids teleocidin and dihydroteleocidin B are also potent inhibitors of [3H]PDBU binding to cultured cells (57). It was of interest to analyze aplysiatoxin and debrómoaplysiatoxin for similar activity. Initially we used CREF cells, since we have previously characterized in detail the specific binding of [3H]-PDBU to receptors in monolayer cultures of these cells (19). Chart 2A indicates that [3H]PDBU binding to intact CREF cells was inhibited by teleocidin, aplysiatoxin, and debrómoaplysiatoxin at 37°. Teleocidin and aplysiatoxin are essentially equipotent in inhibiting [3H]PDBU binding, whereas debrómoaplysiatoxin was much weaker. Very similar results were obtained when inhibition of [3H]PDBU binding to the mouse embryo fibroblast cell line C3H10T1/2 was measured (Chart 2B). In addition, all 4 compounds inhibited [3H]PDBU binding to C3H10T1/2 cells when the assay was conducted at 4° (data not shown here), suggesting a direct physical effect, rather than an indirect effect via cellular metabolism. The doses of each compound required to produce 50% inhibition at 37° (ED50) are given in Table 1. We have also measured the ED50s in CREF cells for purified teleocidin B and lyngbyatoxin A and their catalytically hydrogenated derivatives, dihydroteleocidin B and tetrahydrolyngbyatoxin A. These values were 11, 8, 26, and 18 nm, respectively. Previously we have found that the ED50 for TPA is about 6 nm in CREF cells (57).

Elsewhere, we have studied [3H]PDBU binding to both of these cell types by Scatchard analysis. With CREF, the data were compatible with 2 classes of binding sites, the first with a Kd of 7.6 nm and about 1.6 × 10^6 sites/cell and the second with a Kd of 710 nm and about 2.8 × 10^6 sites/cell (19). The results obtained with C3H10T1/2 cells were also compatible with 2 classes of binding sites, the first with a Kd of 16 nm and about 1.1 × 10^7 sites/cell and the second with a Kd of 1 μM and about 1.7 × 10^7 sites/cell.8

Inhibition of [125I]EGF Binding. TPA inhibits binding of [125I]EGF to the EGF receptor in diverse cell types (5, 24, 33, 34, 37, 40, 43, 45, 57). It has been previously established that the mechanism of inhibition is indirect (19, 34, 35, 45), and not due to binding of EGF and PDBU to the same receptor site. The inhibition does not occur at 4° or in an isolated membrane fraction (34, 35, 45), nor does EGF inhibit [3H]PDBU binding. Nevertheless, the ability of phorbol esters to inhibit [125I]EGF binding correlates quite well with tumor-promoting activity and their ability to inhibit [3H]PDBU receptor binding (5, 24, 26, 33, 37, 40, 45). We have found that teleocidin, aplysiatoxin, and debrómoaplysiatoxin were also effective in inhibiting [125I]EGF-receptor binding in both CREF and C3H10T1/2 cells (Chart 3; Ref. 57). Their relative potencies paralleled their order of potency in inhibition of [3H]PDBU binding (Table 1). Debrómoaplysiatoxin was approximately 10-fold weaker than the other 2 compounds, aplysiatoxin and teleocidin. In all cases, inhibition of [125I]EGF binding required lower concentrations of the compounds than did inhibition of [3H]PDBU binding. We have previously observed this difference with other compounds (20, 21). This phenomenon is not unusual in receptor systems (see, for example, Refs. 1, 25, 27, 49), although the precise explanation is not known (20). It could arise from one of 2 causes: (a) as discussed above, it

---

appears that in both cell types studied, \[^{3}H\]PDBU binds to at least 2 classes of receptor sites, as demonstrated by Scatchard analysis (19); (b) the assays may measure indirect effects of phorbol ester binding. We have previously shown that phorbol ester-induced inhibition of \[^{125}I\]EGF binding does occur by an indirect mechanism (Refs. 34 and 35; see above), although we do not know whether it is mediated by a second messenger or by some other mechanism (e.g., a change in membrane structure or an enzymatic reaction).

**Stimulation of Release of \[^{3}H\]Choline and \[^{3}H\]Arachidonic Acid Metabolites from Prelabeled Cells.** We previously reported that one of the early effects of phorbol esters on C3H10T½ cells is stimulation of release of choline from prelabeled cellular phospholipids (39). Dihydroteleocidin B and lyngbyatoxin A have also been shown to stimulate choline turnover in HeLa cells (44). It was of interest, therefore, to examine the effects of teleocidin, alysiasatoxin, and debromoapisatoxin on choline release from both prelabeled C3H 10T½ and CREF cells. The results are shown in Chart 4. All 3 compounds were approximately equipotent in stimulating choline release into the medium. The ED₅₀’s are summarized in Table 1. In contrast to the results obtained on inhibition of \[^{3}H\]PDBU and \[^{125}I\]EGF receptor binding, alysiasatoxin and debromoapisatoxin were approximately equipotent in inducing choline release in both C3H10T½ and CREF cells. These experiments were repeated 3 times and similar results were obtained each time.

TPA and other tumor-promoting phorbol esters stimulate the release of arachidonic acid from cellular phospholipids, and this is associated with increased prostaglandin synthesis in many cell types (36, 38, 44, 62). Teleocidin B, lyngbyatoxin A, and dihydroteleocidin B have previously been shown to stimulate arachidonic acid release and prostaglandin production in C3H10T½ (57) and HeLa (44) cells. Chart 5 displays the effects of teleocidin, alysiasatoxin, and debromoapisatoxin on \[^{3}H\]arachidonic acid release from prelabeled phospholipids in C3H10T½ cells. The extent and concentration dependence of arachidonic acid release were approximately the same for all 3 compounds. We also found that during the initial 3 hr, the time courses of radioactivity release in C3H10T½ cells were also the same for all 3 compounds (data not shown here). As in the choline release experiments, alysiasatoxin and debromoapisatoxin had similar potencies (Chart 4; Table 1). For reasons that are not apparent, TPA,
Receptor Binding of Aplysia toxin and Teleocidin

![Graph showing release of [3H]arachidonic acid metabolites from C3H10T1/2 cells.](image)

**Chart 5.** Release of [3H]arachidonic acid metabolites from C3H10T1/2 cells. •, teleocidin stimulation; ○, aplysia toxin stimulation; and •, debromoaplysiaxin stimulation. Data from a single representative experiment are shown. Points, average of duplicate plates. Qualitatively similar results were obtained in 2 additional studies.

Aplysia toxin and debromoaplysiaxin did not stimulate arachidonic acid release in CREF cells under the conditions used in the present study.

**DISCUSSION**

The similar effects of teleocidin, polyacetates, and the phorbol ester tumor promoters in several biological systems described in this study and in previous studies (see “Introduction”) suggest that these 3 classes of compounds act by the same or very similar mechanisms (11, 14). Since all 3 classes of compounds inhibit binding of [3H]PDBU to high-affinity cellular receptors, it is likely that they all produce at least some of their pleiotropic effects by binding to these receptors. The inhibition of [3H]PDBU binding by teleocidin, aplysiaxin, and debromoaplysiaxin appears to be a direct effect since it occurs at both 37 and 4°C, and was also seen when binding was studied with an isolated membrane fraction. Because the chemical structures of these compounds appear quite dissimilar (Chart 1), these results stimulated us to examine the possibility that these 3 classes of compounds share structural elements which allow them to interact with similar binding sites on the putative membrane-associated receptor.

X-ray structural data are available for TPA and dihydroteleocidin B (4, 15), but not for aplysiaxin and debromoaplysiaxin, making a detailed comparison of structures of the 4 compounds difficult. All 4 compounds contain a number of heteroatoms. In TPA, there is considerable evidence that an unsaturated keto group at C-3, a primary allylic hydroxyl at C-20, a nonmethylated hydroxyl at C-4, and a highly hydrophobic ester at C-12 are necessary for maximum activity (16, 59, 63). The carbonyl, amino, and hydroxyl groups in teleocidin, as well as the indole nitrogen (Chart 1), may play roles similar to these functional groups in TPA in binding to the PDBU receptor. In addition, teleocidin B contains a hydrophobic region (C-14 to C-23; see Chart 1) which may play a role similar to that of the hydrophobic ester at C-12 in TPA. Although the teleocidin sample used in these experiments contains epimers of teleocidin A and B, the variations in structure occur in what is probably the least critical region of the molecule, the side chains of the hydrophobic region (C-14 to C-23). Experiments with the phorbol esters and related plant diterpenes suggest that considerable variation in the structure of the hydrophobic groups attached to C-12 and C-13 of TPA, which in our model corresponds to the region C-14 to C-23 of teleocidin, may occur without abolishing biological activity or receptor binding, although the potency of the phorbol esters does depend on the nature of the hydrophobic group (16, 20, 30-32, 59, 63). It appears that these regions of the phorbol esters and teleocidin interact by rather nonspecific binding to a hydrophobic region of the phorboid receptor or to its lipid microenvironment. However, we suggest that the above-mentioned carbonyl, hydroxyl, and amino groups of the phorbol esters and of teleocidin interact specifically with complementary residues in the binding site of the phorboid receptor. This would explain the marked sensitivity of the activity of phorbol derivatives with respect to the orientation of the 5- and 7-membered rings to each other and to modification of these functional groups (12, 16, 20, 59, 63).

Aplysiaxin and debromoaplysiaxin contain several carbonyl and hydroxyl groups (Chart 1) which may play a role similar to that of the hydrophobic domain in phorbol esters does depend on the nature of the hydrophobic group (16, 20, 30-32, 59, 63). It appears that these regions of the phorbol esters and teleocidin interact by rather nonspecific binding to a hydrophobic region of the phorboid receptor or to its lipid microenvironment. However, we suggest that the above-mentioned carbonyl, hydroxyl, and amino groups of the phorbol esters and of teleocidin interact specifically with complementary residues in the binding site of the phorboid receptor. This would explain the marked sensitivity of the activity of phorbol derivatives with respect to the orientation of the 5- and 7-membered rings to each other and to modification of these functional groups (12, 16, 20, 59, 63).

We must stress that the above models for receptor binding are highly speculative and do not in themselves explain all of the structure-activity relationships elucidated with various phorbol esters and related macrocyclic diterpenes (16, 59, 63). More detailed studies of additional compounds, as well as information on their stereochemistries, are required to confirm or modify these models. In addition, we should emphasize that the present receptor-binding data are based entirely on inhibition of [3H]PDBU binding. When radioactive teleocidin, aplysiaxin, and debromoaplysiaxin become available it will be important to measure their binding capacities directly.

The [3H]PDBU- and [125I]EGF-binding data obtained in the present study support the idea that the phorbol esters, indole alkaloids, and polyacetates bind to and act through a common set of receptors, although it appears that debromoaplysiaxin binds much more weakly to this receptor than do the other...
compounds. This conclusion is consistent with several previous studies (10, 11, 14, 22, 23, 42, 44, 50–54, 57, 61). It was surprising, therefore, to find that debromoaplysiatoxin was equipotent with teloecladin and aplysiaxatin in stimulating [H]choline and [3H]arachidonic acid release from C3H10T½ cells and [3H]choline release from CREF cells (Table 1). Furthermore, debromoaplysiatoxin stimulates choline and arachidonic acid release at a concentration far below that at which it appears to bind to the receptors occupied by [3H]PDBU (Table 1). A similar disparity in the concentrations of debromoaplysiatoxin required to produce certain other biological effects has been noted earlier (14, 50–54). These results suggest that induction of arachidonic acid and choline release by debromoaplysiatoxin is mediated by a set of receptors distinct from the class measured by [3H]PDBU binding and the class involved in inhibition of [3H]EGF binding, although other explanations have not been excluded. The high-affinity class of phorbol receptors measured by [3H]PDBU binding appears to comprise about 2 × 10⁶ sites per cell in CREF cells (19), which is a very large number of sites for a hormone receptor. There could be a second high-affinity class of receptors with fewer binding sites per cell, whose presence might be masked by the large amount of binding to the first-class of phorbol receptors, and the second class might preferentially bind debromoaplysiatoxin, and perhaps other unidentified compounds. Alternatively, the effects of phorbol esters, teloecladin, and aplysiaxatin on phospholipid metabolism might result from direct interaction of these compounds with the membrane lipids, although such interaction would also have to be quite specific.

In either case our results strongly suggest that the binding of phorbol esters, choline, and aplysiaxatin to cellular receptors involves a greater heterogeneity of receptors or binding sites than previously realized. This heterogeneity could explain the subtle variations in the biological activities among these compounds, as well as some of the variations among various cell types in their responses to the same compounds (20, 60).

ACKNOWLEDGMENTS

The authors would like to thank Dr. Frederick Kramer for valuable assistance with the computer graphics aspect of this study, Patricia Kelly for her valuable assistance in preparing the manuscript, and John Mack for the illustrations of molecular structures. Dr. Hiroto Fujiki thanks the United States-Japan Cooperative Medical Science Program for funds to carry out the collaborative work with the Cancer Center/Institute of Cancer Research of Columbia University.

REFERENCES

Receptor Binding of Aplysiatoxin and Teleocidin

Comparative Effects of Aplysiatoxin, Debromoaplysiaotoxin, and Teleocidin on Receptor Binding and Phospholipid Metabolism


Updated version  Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/43/4/1529

E-mail alerts  Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions  To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions  To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.