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# Peptides with anticancer use or potential

*Review Article*

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**Summary.** This review is an attempt to illustrate the diversity of peptides reported for a potential or an established use in cancer therapy. With 612 references, this work aims at covering the patents and publications up to year 2000 with many inroads in years 2001–2002. The peptides are classed according to four categories of effective (or plausible) biological mechanisms of action: receptor-interacting compounds; inhibitors of protein-protein interaction; enzymes inhibitors; nucleic acid-interacting compounds. The fifth group is made of the peptides for which no mechanism of action has been found yet. Incidentally this work provides an overview of many of the modern targets of anticancer research.

**Keywords:** Peptides – Antitumor

## I Introduction

This review is an attempt to illustrate the diversity of characterised peptides reported for a potential or an established use in cancer therapy. The origin and *raison d'être* of this work stemmed from the coincidence described here:

In 1995, the co-crystallisation of Ras binding domain of Raf-1 and Rap-1 (a protein related to oncogenic protein Ras) enabled an X ray analysis of the interacting amino acids residues (Nassar et al., 1995). One interesting feature of protein Rap-1 binding domain is the sequence 37–39: **Glu-Asp-Ser**. These residues not only follow each other on the peptide backbone but the two carboxylic residues are also involved in very strong ionic interactions with Raf positively charged guanidinium residues; namely Arg-59 and Arg-89. Thus, it could be proposed that small peptides containing the motif Glu-Asp-Ser were potential Ras-Raf interaction inhibitors and hence potential leads for an anticancer medicinal chemistry research project. This starting point was followed by some literature search which came out with the remarkable fact that the pentapeptide pGlu-**Glu-Asp-Ser-**Gly is an inhibitor of epidermal mitoses (Jensen et al., 1990). This fact probably led to the simultaneous development of two analogues by pharmaceutical companies as cell proliferation inhibitors (Balazs et al., 1992; Laerum, 1990). However, despite some trials, we could not confirm the inhibition of Ras-Raf interaction as the actual mechanism of this antiproliferative action. If nothing, this curiosity pointed out a possible need for a review of peptidic derivatives with an actual or a potential use in antitumor therapy; especially since this type of substance is more and more often a starting point in medicinal chemistry (Mizejewski, 2001).

Only a handful of peptides, such as the LH-RH agonists and somatostatin analogues, are actually used as anticancer drugs (Loffet, 2002). Even if more compounds are currently at various clinical trials stages (Jimeno, 2002), peptides even only reported for a cytotoxicity, an antiproliferative action or displaying a potentially useful effect were included in this review. Indeed, the low bioavailability of peptides can restrict their action to cell culture or even to molecular mechanism models and thus seriously hamper any pharmaceutical potential. However, we thought that enlarging our search to as many peptides as possible and thus to as many molecular mechanisms as possible would still be of interest. We excluded all the "large" proteins,

the main reason being an organic chemist point of view, since preparation and use of these cytokines for cancer therapy has become one of the many achievements of the molecular biochemists (Maini et al., 1997; Mueller, 1998; Oppenheim et al., 1997). The many peptidic substances involved in the stimulation of an immune response to cancer (Velders et al., 1998) were excluded as well as the peptide-containing prodrugs and the amphipatic peptides better known for their antimicrobial properties (Jacob and Zasloff, 1994) than for their antitumor potentials (Shin et al., 1999). The present manuscript aims at covering the patents and publications up to year 2000 with many inroads in years 2001–2002. The peptides are classed according to four categories of effective (or plausible) biological mechanisms of action: receptor-interacting compounds; inhibitors of protein-protein interaction; enzymes inhibitors; nucleic acid-interacting compounds. The fifth group is made of the peptides for which no mechanism of action has been found yet. Concerning this last group, the yearly reviews of D. J. Faulkner on marine natural products illustrate quite well the number of naturally-occurring cytotoxic peptides reported (Faulkner, 2002). However it was beyond the scope of this review to compare their respective level of cytotoxicity (if such thing is possible given the many different test used) or even to depict all the substances isolated.

## II Receptor-interacting compounds

### *II.1 Luteinizing hormone-releasing hormone agonists and antagonists*

In 1971 the decapeptidic structure of a luteinizing hormone-releasing hormone (LH-RH)/Gonadotrophin-releasing hormone (pGlu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-$NH_2$) was reported (Schally, 1999). This is one of the hormonal messages issued from the hypothalamus to the pituitary gland. Its action leads to the release of luteinizing hormone and follicle-stimulating hormone which acts on ovaries and testes, and thus, on the release of steroidals hormones. Synthesis of many analogues led to structure-activity relationships which were reviewed (Dutta, 1988a; Dutta, 1988b; Kutscher et al., 1997). Compounds currently used in hormonal therapies such as treatment of sex hormone-dependent malignant neoplasms lead to objective stable disease or partial remission (Hoffken and Kath, 2000; Schally, 1999). A noteworthy feature is that the agonists currently used were found by "simply" replacing the glycine moiety in position 6 with various D-amino acids such as D-Trp, D-Leu or D-Ser. This change not only confers a stability toward the protease that quickly hydrolyses LH-RH but also a receptor affinity increase. A review (Kutscher et al., 1997) describes the remarkable and much more important structural changes necessary to obtain potentially useful (Huirne and Lambalk, 2001) antagonists such as cetrorelix (Fig. 1) (Reissmann et al., 1994). Other antagonist described are for example a Nal-Glu derivative (Rivier et al., 1986), ganirelix (Nestor et al., 1992) or abarelix (Molineaux et al., 1998). As described in a recent article, present research is focused on the design of long-acting antagonists (Jiang et al., 2001).

### *II.2 Mammalian gastrin-releasing peptide (bombesin) analogues*

The human 27-mer peptide named Gastrin-releasing peptide (GRP), unlike the amphibian-originated tetradecapeptide bombesin (pGlu-Gln-Arg-Leu-Gly-Asn-Gln-Trp-Ala-Val-Gly-His-Leu-Met-$NH_2$), is a neuronal-originated hormone. Initially, both compounds were found to trigger the gastrin release *in vivo*. However, even if many other physiological actions were later found, the original names perpetuate. Bombesin and GRP share important sequence homologies and, based on immunology or gene cloning, searches for other human endogenous peptides were made. From this, emerged a picture (de Castiglione and Gozzini, 1996; Preston et al., 1996) involving, so far, two different peptides: the 27-mer GRP (Battey and Wada, 1991) and the 32-mer neuromedin B (Ohki-Hamazaki, 2000). Moreover, as three different mammalian receptors have been found (Nagalla et al., 1995; Preston et al., 1996), a specific

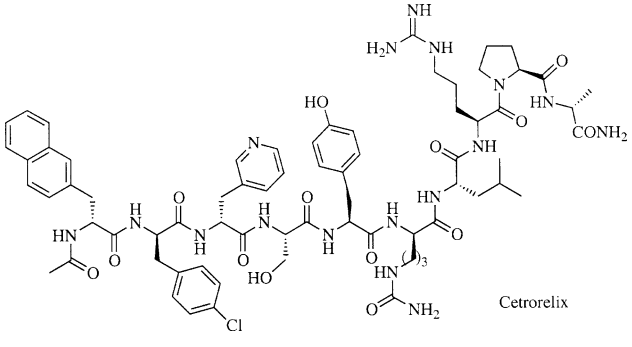



**Fig. 1.** Structure of Cetrorelix

endogenous ligand for the third type remain to be characterised (Ryan et al., 1998). The structural characteristics of the many known agonists were reviewed (Lin et al., 1995; Raynor et al., 1993) and recent works focus upon the determination of the receptor's residues involved in ligand binding (Sainz et al., 1998; Tokita et al., 2001). More than 10 years ago, it was recognised that the GRP secreted by malignant cells such as small cell lung cancer (SCLC) and medullary thyroid carcinoma could act as an autocrine/paracrine growth factor. This would explain some early results such as the mitogenic action of GRP on fibroblast cell line Swiss 3T3 or its *in vitro* growth action on SCLC (Cuttitta et al., 1985; Moody et al., 1981). More recently, neuromedin B was found to have a similar effect (Cardona et al., 1991). The search for antagonists with a potential use in anticancer treatment was thus rationalised. The first antagonists, which have peptidic structures based either on bombesin, litorin or substance P, have been shown (Thomas et al., 1992) to partially inhibit tumour growth in SCLC xenografted nude mice and were reviewed (de Castiglione and Gozzini, 1996). Since then, more compounds active *in vivo* have been reported (Burman et al., 2002; Burman et al., 2001a; Everard et al., 1993; Langdon et al., 1992; Matsumoto et al., 2000; Orosz et al., 1995; Reile et al., 1995). As an illustration, the short analogues D-(NMe)Phe-D-Trp-Phe-D-Trp-Leu Ψ ($CH_2NH$)Leu-$NH_2$ or derivatives of Phe-D-Trp-Phe-D-Trp-Leu-Leu were reported (Nyeki et al., 1998; Orosz, 2001; Orosz et al., 1994) and the antagonist RC-3095 (Radulovic et al., 1991), (Fig. 2) which bears a reduced bond between the two C-terminal leucines, was found active on a whole array of tumour models (de Castiglione and Gozzini, 1996).

Recent works and current hypothesis (Ohlsson et al., 1999; Petit et al., 2001), which were reviewed recently (Heasley, 2001), point out the possible role of many other neuropeptides (i.e.: neurotensin, gastrin, cholecystokinin or arginine vasopressin) as autocrine/paracrine factors of tumour growth. Whether the use of finely tuned antagonists or the use of compounds active on a broad spectrum of neuropeptide receptors provide the best objective response will hopefully be determined in the future (Heasley, 2001; Sethi et al., 1992).

### *II.3 Somatostatin analogues*

Somatostatin was initially isolated from ovine hypothalami and described as a regulator of growth hormone secretion (Brazeau et al., 1973; Krulich et al., 1968). It was later demonstrated that the multiple effects caused by somatostatin are mediated by at least five somatostatin receptors (Lamberts et al., 1996; Patel et al., 1995). Thus, actions of somatostatin are seen on neurotransmission in the central nervous system, on the regulation of growth hormone and on thyrotropin release (Reichlin, 1983). It has also multiform regulatory roles on the gastrointestinal tract and on the pancreas. Two important bioactive somatostatins exist, the sulfide-bridged tetradecapeptide somatostatin 14: Ala-Gly-Cys-Lys-Asn-Phe-Phe-Trp-Lys-Thr-Phe-Thr-Ser-Cys, and somatostatin 28, which is extended by 14 more residues from the aminated end of somatostatin 14. With the necessity to dispose of more stable somatostain receptor agonists, the first "wave" of syntheses led to many analogues (Bauer et al., 1982; Cai et al., 1986; Kéri et al., 1993; Murphy et al., 1985; Raynor et al., 1993; Taylor et al., 1988; Veber et al., 1981). Amongst them are established anticancer drugs such as octreotide or somatuline (Fig. 3) (Bauer et al., 1982; Bogden et al., 1990; Lamberts et al., 1996). Both

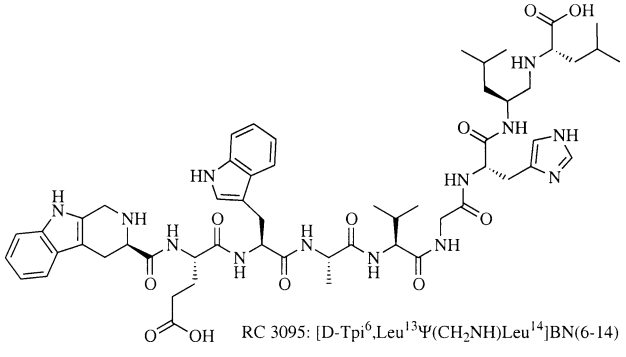



**Fig. 2.** Structure of the bombesin-derived antagonist RC 3095

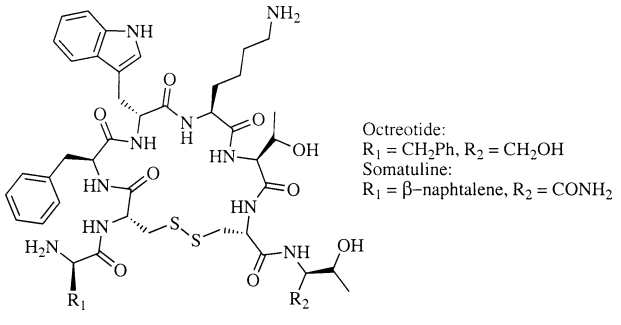



**Fig. 3.** Structure of octreotide and somatuline

compounds are bearing a $\beta$-turn feature, made by Phe-D-Trp-Lys-Thr, which is crucial for the activity.

The current second "campaign" of research of subtype-specific receptors (Weckbecker et al., 1993) agonists and antagonists (Bass et al., 1996; Bass et al., 1997; Gazal et al., 2002; Hocart et al., 1999; Morgan and Sadat-Aalaee, 2001) could lead to a better understanding of somatostatin roles and possibly much more specific treatments (Bousquet et al., 2001). A recent approach, replacing $\alpha$-amino acids with $\beta$-amino acids, met success as a linear $\beta$-peptide (Fig. 4) was found to have a strong and specific affinity for somatostatin subtype 4 receptor (sst-4) (Gademann et al., 2001). Another noteworthy compound is a cyclic disulfide (Fig. 4) which was found to be an antagonist of somatostatin (Hocart et al., 1999).

Moreover, although somatostatin analogue therapy has its importance (Eriksson and Oberg, 1999), all tumour growth become eventually unresponsive to the treatment. Thus, further strategies based on specific targeting of toxic substances – possibly $^{90}$Ytterbium or other radio-labelled compounds (Albert et al., 1998; Heppeler et al., 2000; Kwekkeboom et al., 2000; Oberg, 2001; Szegedi et al., 1999) – may lead to new protocols (Eriksson and Oberg, 1999).

### *II.4 Less investigated examples*

*II.4.1 Growth hormone-releasing hormone.* The growth hormone-releasing hormone (GH-RH) peptide belongs to a group of structurally related hormones that includes vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide, secretin and glucagon (Campbell and Scanes, 1992).

– From the structure of GH-RH, a 29-mer antagonist was found to have an *in vivo* antitumor effect on nude mice bearing xenografts (Kiaris et al., 1999; Varga et al., 1999). However, the actual mechanism of action of this antagonist may be more complex (Kineman, 2000). Concerning the 28-mer VIP, the presence of VIP receptor in non-small cell lung cancer led to the design of an antagonist. This peptide is made of a 22 amino acids-long segment of VIP linked with an N-terminal sequence (Lys-Pro-Arg-Arg-Pro-Tyr), added to increase its cell membrane permeability. This antagonist significantly inhibited xenograft formation in nude mice (Moody et al., 1993). More recently, longer unnatural peptides were patented for sub nanomolar cytotoxicities (Burman et al., 2001b).
– A 33-mer fragment of pituitary adenylate cyclase-activating polypeptide was also reported to inhibit the growth of prostate cancer cells bearing the corresponding receptor (Leyton et al., 1998). Recent works have focused on the preparation of more specific antagonists (Rekasi et al., 2000).

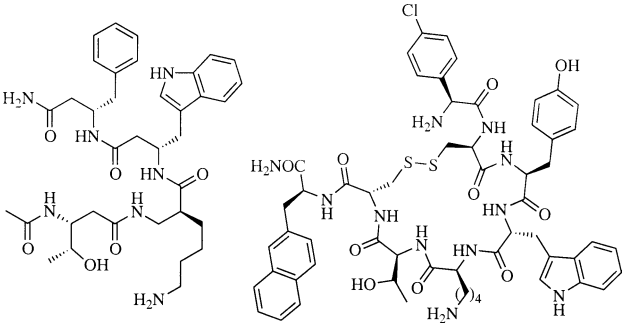


**Fig. 4.** The first $\beta$-peptide ligand of sst-4 and an antagonist of somatostatin

*II.4.2 Vascular endothelial growth factor.* Inhibition of the vascular endothelial growth factor (VEGF) signalling abrogates the development of many tumors (Neufeld et al., 1999). From a peptide library, some arginine-rich hexapeptides were found to inhibit the interaction between $VEGF_{165}$ and the VEGF receptor (Bae et al., 2000). For example, on a nude mice model, the peptide Arg-Arg-Lys-Arg-Arg-Arg prevented the growth and metastasis of the VEGF-secreting HM7 human colon carcinoma cells. Other peptides were also patented (Schatz et al., 2001). Another three different classes of disulfide-bridged peptide capable of inhibiting VEGF interaction with its receptor were found starting from a phage display method (Fairbrother et al., 1998). In a different approach, an inhibition of the interaction between VEGF and VEGF receptor-2 by the peptide Ala-Thr-Trp-Leu-Pro-Pro-Arg leads to a proliferation inhibition (Binétruy-Tournaire et al., 2000). Moreover, the 18-mer Arg-Thr-Glu-Leu-Asn-Val-Gly-Ile-Asp-Phe-Asn-Trp-Glu-Tyr-Pro-Ala-Ser-Lys, also derived from VEGF receptor 2, inhibits proliferation and migration of microvascular endothelial cells at a micromolar concentration (Piossek et al., 1999). Other peptides, such as His-His-Glu-Val-Val-Lys-Phe-Met-Asp-Val-Tyr-Gln which is derived from the exon 6 sequence of VEGF, were also reported for their inhibition of endothelial cell responses (Jia et al., 2001). Finally, the small peptide Asn-Ile-Thr-Val-Thr-Leu-Lys-Lys-

Phe-Pro-Leu, derived from the sequence of VEGF receptor-1, was reported recently as an angiogenesis inhibitor although this peptide does not bind VEGF nor inhibits its binding to the corresponding receptor (Tan et al., 2001).

*II.4.3 Epidermal growth factor.* Some cyclic disulfide peptides, derived from the epidermal growth factor (EGF), such as Cys-His-Ser-Gly-Tyr-Val-Gly-Val-Arg-Cys were patented for their inhibitory activity of EGF-induced cell proliferation (Nestor et al., 1985). Moreover the peptidic motifs Leu-Gly-Leu-Arg-Ser-Leu-Arg-Glu or Leu-Gly-Leu-Arg-Ser-Leu-Lys-Glu were claimed to antagonise the EGF receptor (Lupu and Lippman, 1994). Fairly more complex compounds bearing three disulfide bridges (a T-knot feature) were also found to antagonise the EGF (Blanco-Aparicio et al., 1998). In a different approach, the product of HER2, which is also a member of the EGF family, was found to be inactivated by small peptides mimicking antibodies such as trastuzumab (Herceptin). Thus, the dodecapeptide Tyr-Cys-Asp-Gly-Phe-Tyr-Ala-Cys-Tyr-Met-Asp-Val-$NH_2$ binds to the HER2 receptor and antagonises its constitutive growth signalling properties *in vitro* (Berezov et al., 2001). A recent review of inhibitors of the EGF receptor as potential anticancer compounds describes other approaches (Woodburn, 1999).

*II.4.4 Interleukin 6.* Antagonists hindering the binding of interleukin 6 to its receptor were found using phage display techniques. Further modifications from the consensus sequence led to the cyclic disulfide peptide Gly-Gly-Cys-Lys-Leu-Trp-Thr-Ile-Pro-Glu-Cys-Gly-Gly which inhibited cellular growth (Mizuguchi et al., 2000).

*II.4.5 Interleukin 8.* A hexapeptide (Ac-Arg-Arg-Trp-Trp-Cys-Arg-$NH_2$) which inhibits the binding of interleukin 8 to neutrophiles was found (Hayashi et al., 1997) to also inhibit the growth of melanoma cell lines stimulated by a 73-mer $\alpha$-chemokine. This peptide is active *in vivo* as well (Fujisawa et al., 1999). On the other hand, the $NH_2$-terminal pentapeptide corresponding to endothelial interleukin 8 (Ala-Val-Leu-Pro-Arg) is responsible for apoptosis induction and has an antitumor effect *in vivo* (Terui et al., 1999).

*II.4.6 Platelet-derived growth factor.* The octadecapeptide Tyr-Gly-Arg-Pro-Arg-Glu-Ser-Gly-Lys-Lys-Arg-Lys-Arg-Lys-Arg-Leu-Lys-Pro-Thr is a fragment of the platelet-derived growth factor and was found to inhibit the growth of malignant glioma in athymic nude mice (Khachigian et al., 1995).

*II.4.7 Tumour necrosis factor.* Cyclic analogues of tumour necrosis factor, such as the cysteine-bridged Ac-Cys-Pro-Ser-Glu-Gly-Leu-Cys-$NH_2$ and Ac-Cys-Pro-Ser-Glu-Gly-Thr-Pro-Ser-Thr-His-Val-Leu-Cys-$NH_2$, were patented (Boehm et al., 1990c). The same research group also patented linear peptides such as Ac-Leu-Ala-Asn-Gly-Val-Glu or Pro-Gln-Ala-Glu-Gly-Gln-Leu-$NH_2$ for their tumour necrosis factor agonist or antagonist activities (Boehm et al., 1990a; Boehm et al., 1990b). The related sequence Val-Ala-Asn-Pro-Gln-Ala-Glu-Gly-Gln-Leu had actually been patented previously (Furuta and Hayashi, 1986). Moreover, cyclic peptides containing the murine tumour necrosis factor amino acids sequence 127–132 (cyclic Lys-Gly-Asp-Gln-Leu-Ser) or 59–66 (cyclic Tyr-Ser-Cln-Val-Leu-Phe-Lys-Gly) were found to have a weak cytotoxicity (Sheh et al., 1990; Sheh et al., 1993).

*II.4.8 Alpha-feto protein.* The octapeptide Glu-Met-Thr-Pro-Val-Asn-Pro-Gly, derived from the 590-mer alpha-feto protein, was shown to retain all the inhibition capacity against estrogen-dependant growth of human breast cells. Further work demonstrated that this peptide would undergo a time-dependant activity loss via a hydrophobic-based self aggregation phenomenon. The substitution of the two lipophilic prolines residues with the more polar 4-hydroxy prolines led to a stable analogue which is an inhibitor of the estrogen-dependant growth of MCF-7 human breast cancer (Mesfin et al., 2001). Remotely related to this approach is a recent patent which reports peptides, found by a phage-display technique, that mimick the biological activity of steroid hormones (Kohen et al., 2002).

*II.4.9 Sialyl-Lewis mimics.* Peptidic derivatives mimicking sialyl-Lewis carbohydrates were recently found using, respectively, combinatorial chemistry and phage display techniques (Fukuda et al., 2000; O et al., 1999). One of the peptide (Ile-Glu-Leu-Leu-Gln-Ala-Arg) inhibits the sialyl Lewis X-dependent lung colonisation of tumour cells *in vivo* by antagonising the selectin receptors (Fukuda et al., 2000).

## III Inhibitors of protein-protein interaction

This section concerns compounds able to block cancer-related biological processes involving a protein-protein interaction (Huber et al., 1994). Many peptides should be placed in this section although either the actual interaction inhibited has not been

found or has not been recognised as such yet. Moreover the distinction between this class and the receptor-interacting class is somewhat arbitrary since what is the difference between two interacting proteins and the binding of a protein to its receptor?

### *III.1 Urokinase-type plasminogen activator interfering compounds*

Cell migration and invasiveness are crucial steps in cancer where tissue remodelling, angiogenesis and metastasis and leading to critical situations. The serine protease urokinase-type plasminogen activator (uPA) and its cell surface urokinase plasminogen activator receptor (uPAR) are central to these processes (Andreasen et al., 1997; Mazar, 2001; Reuning et al., 1998; Weidle and Koenig, 1998). Interaction between the uPA and uPAR not only enables the activation of plasmin (via cleavage of the proenzyme plasminogen) but also focuses the plasmin proteases activity on the cell surface. A review further describes the complexity of this activation system in which some components have been found to be relevant indicators for patient prognosis in human cancer (Reuning et al., 1998).

Thus inhibition of the uPA/uPAR interaction was the focus of some research (Fazioli and Blasi, 1994; Frankenne et al., 1999). Peptides related to the 18–32 amino acids sequence of uPA, which is involved in the binding with uPAR (Bürgle et al., 1997), were found to have an effect on *in vitro* and *in vivo* invasiveness models (Kobayashi et al., 1994a; Kobayashi et al., 1993). The disulfide-bridged cyclic tridecapeptide $uPA_{19–31}$ (Cys-Val-Ser-Asn-Lys-Tyr-Phe-Ser-Asn-Ile-His-Trp-Cys) has been suggested as a lead for further development of antagonists (Bürgle et al., 1997). On the other hand, phage display-based research led to the discovery of a group of short peptides (subsequence motifs Phe-X-X-Tyr-Lys-Trp or Lys-Trp-X-X-Ar; Ar being Tyr, Phe, His or Trp), unrelated to the above-mentioned uPAR binding sequence, that antagonise the uPA/uPAR interaction (Goodson et al., 1994). The same research group reported that compounds as short as the decapeptide Leu-Asn-Phe-Ser-Gln-Tyr-Leu-Trp-Tyr-Thr-$NH_2$ retained affinity in the nanomolar range for the uPAR (Tressler et al., 1999). It is noteworthy that the tumour growth inhibition observed in some cases may also be caused by the peptide promotion of the binding of uPAR cell-bearing to vitronectin (Tressler et al., 1999). Peptides containing Ser-Arg-Ser-Arg-Tyr, also corresponding to a uPAR sequence, were patented (Blasi et al., 1998). And an octapeptide derived from another non receptor binding region of uPA (Ac-Lys-Pro-Ser-Ser-Pro-Pro-Glu-Glu-$NH_2$) was found to be a non competitive inhibitor of tumour progression and angiogenesis *in vivo* (Guo et al., 2000; Mishima et al., 2000).

### *III.2 p53 (Hdm2, $p14^{ARF}$ and p53 C-terminal regulatory domain)*

Mutations on the p53 gene or of the proteins that regulates p53 have been found in at least 80% of all human tumours (Helmreich, 2001). The key role of this protein is indeed the prevention, or the postponing, of the multiplication of DNA-damaged cells such as cancerous one. Accordingly, compounds able to restore p53 function – to rescue it pharmacologically (Foster et al., 1999) – could act alone, or in concert with classical DNA-damaging anticancer agent, as remarkably original approaches to anticancer treatment. Several research avenues involving p53 were recently reviewed (Hupp et al., 2000).

– The protein Hdm2 (Human double minute 2) or its murine equivalent Mdm2 were suggested to be responsible for the (necessary) cellular degradation of p53, via a binding to its N-terminus part, followed by ubiquitin-dependent proteolysis (Böttger et al., 1996; Lane and Hall, 1997). An overexpression of this protein would thus disrupt the normal function of p53. Accordingly, an approach started with the sequence of p53 Hdm2-binding site: Thr-Phe-Ser-Asp-Leu-Trp (Böttger et al., 1997). Since this peptide was only a very weak inhibitor of the interaction, a phage display-based search was conducted and led to the more active inhibitor Ac-Met-Pro-Arg-Phe-Met-Asp-Tyr-Trp-Glu-Gly-Leu-Asn-$NH_2$ (Böttger et al., 1996). From this, a feat of synthesis, quite driven by X-ray structure-based optimisation, led to very efficient ex vivo antagonists (García-Echeverría et al., 2000; Luke et al., 1999). One of the most active octapeptide (Fig. 5) was shown to stimulate, albeit – because of a low cell permeability – at a high concentrations, the p53 pathway in tumour cell lines (Chène et al., 2000). Curiously, two facts probably open new avenues of research. The first is a patent which claims antitumor peptides, derived from the N-terminal part of p53, that are able to block a p53-retinoblastoma protein interaction

(Kouzarides, 1998). The second is that the first 25 N-terminal amino acids of p53 were recently proven to interact with tubulin (Giannakakou et al., 2000). It is thus tempting to suggest that peptides mimicking the N-terminal moiety of p53 have at least three proteins as potential targets. Moreover, the naturally occurring chlorofusin (Fig. 5), isolated from *Fusarium sp*., was found to be an antagonist of the p53-Mdm2 interaction at micromolar concentration (Duncan et al., 2001).

– One step removed from p53 is the $p14^{ARF}$ protein which binds to Mdm2 and thus indirectly prevents the p53 inactivation. A 20 amino acid-long peptide (Met-Val-Arg-Arg-Phe-Leu-Val-Thr-Leu-Arg-Ile-Arg-Arg-Ala-Cys-Gly-Pro-Pro-Arg-Val) corresponding to the beginning of the $p14^{ARF}$ sequence was recently demonstrated to induce p53 protein and prevent its ubiquitination (Midgley et al., 2000).
– Peptides corresponding to the carboxy-terminal sequence of p53 do restore its growth suppression function (Selivanova et al., 1997). Indeed, peptides derived from the C-terminal amino acids sequence 361–383 (Gly-Ser-Arg-Ala-His-Ser-Ser-His-Leu-Lys-Ser-Lys-Lys-Gly-Gln-Ser-Thr-Ser-Arg-His-Lys-Lys-Leu) of p53 have been patented for their ability to activate p53 function (Halazonetis and Hartwig, 1996; Halazonetis and Hartwig, 2001; Shibata et al., 1999). More is said about this case in the conclusion. These finding could be explained by the proposition that these peptides antagonise proteins which have an affinity for the p53 C-terminal negative regulatory domain (Hupp et al., 2000).

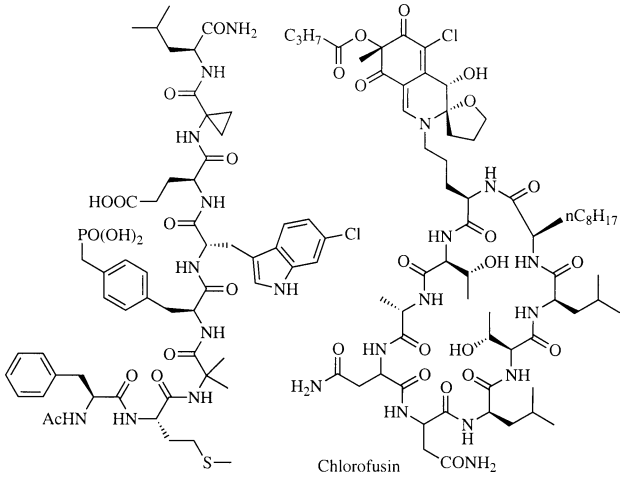



**Fig. 5.** A man-made Hdm2 antagonist and chlorofusin, a naturally occurring one

### *III.3 Inhibitors based on $p34^{cdc2}$ / $p33^{cdk2}$, $p21^{WAF1}$ and $p16^{INK4}$*

It would be beyond the scope of this review to attempt to explain the role of the retinoblastoma related proteins such as p107 and pRb2/p130 in cell multiplication and cancer (Nevins, 2001). These proteins are transcriptionnal regulators that control the genes involved in the cellular cycling from G1 to S phase (Weinberg, 1995). The assembly of a protein complex made of a histone deacetylase-E2F and pRb is an example of how this control takes place. This trimeric structure binds DNA and thus represses its expression. However, if phosphorylation of pRb (by the many cyclin dependant kinase/cyclin complexes) takes place, pRb loses its affinity for E2F and the gene repression is lifted. Thus, these phosphorylation events can be considered as a ternary association of the cyclin, the cyclin dependant kinase and their protein substrates. These associations could be attractive targets for a selective protein-protein inhibition. A recent review further describes the system that regulates cyclin-dependent kinase (Cdk) and its importance for new anticancer drug design (McDonald III and El-Deiry, 2000). As far as we could tell, there are three different avenues of such research that led to peptides which are based either on the serine/threonine kinases $p34^{cdc2}$ / $p33^{cdk2}$, the protein $p21^{WAF1}$ or the protein $p16^{INK4}$.

– Serine/threonine kinases $p34^{cdc2}$ / $p33^{cdk2}$. A patent describes inhibitors of the cell cycle regulatory serine/threonine kinases $p33^{cdk2}$ and $p34^{cdc2}$. These two related kinases are associating with many proteins, including pRb2, p107 and the human papillomavirus oncoprotein E7. Cyclins binding to p34 or p33 is of course required for their kinase activity. The peptides Cys-Ala-Phe-Tyr-Ile, a longer homologue Leu-Cys-Ala-Phe-Tyr-Ile-Met-Ala-Lys, and Met-Cys-Ser-Met-Tyr-Gly-Ile-Cys-Lys, which are derive from the p34 binding domain of pRb2, p107 and cyclin E, were demonstrated to inhibit the interaction of p34 or p33 with these proteins. Hopefully, further work concerning their antitumor potential or their use as biological tools will be reported in the future (Webster and Coleman, 1994).

Another approach led to the anti-Cdk2 aptamer Tyr-ser-Phe-Val-His-His-Gly-Phe-Phe-Asn-Phe-Arg-Val-Ser-Trp-Arg-Glu-Met-Leu-Ala using an *Escherichia coli*-based display method along with the two

hybrids method and was found to inhibit the interaction of Cdk2 with histone H1 but not with pRb (Colas et al., 1996). As expression of this sequence led to the cell-cycle arrest, this work demonstrates a role for histone H1 phosphorylation (Cohen et al., 1998).

– $p21^{WAF1}$. The cdk inhibitor protein p21 is actually one of the gene products, mediating cell growth arrest, that are controlled by p53. This inhibition is achieved via protein-protein interaction between p21 and G1 cyclin-Cdk complexes (Chen et al., 1996). Using a series of 20-mer synthetic peptides that spanned the entire sequence of p21, the peptide Lys-Arg-Arg-Gln-Thr-Ser-Met-Thr-Ala-Phe-Tyr-His-Ser-Lys-Arg-Arg-Leu-Ile-Phe-Ser, closely related to the $p21_{141–160}$ carboxy-terminal domain, was found to inhibit the cyclin D1-Cdk4 at nanomolar level and induced a G1/S growth arrest (Ball et al., 1996). The smaller fragment Lys-Arg-Arg-Leu-Ile-Phe-Ser-Lys did retain some activity. Expression of such peptide as a GFP miniprotein was also used to demonstrate a cell proliferation inhibition (Mattock et al., 2001). Other peptides, derived from two different regions of p21 (but one of them containing an Arg-Arg-Leu-Phe motif), were linked to the carrier/internalising hexadecapeptide sequence found in *Antennapedia* (Arg-Gln-Ile-Lys-Ile-Trp-Phe-Gln-Asn-Arg-Arg-Met-Lys-Trp-Lys-Lys) and were shown to inhibit human cancer cells growth (Bonfanti et al., 1997; Fischer et al., 2000). Further work demonstrated that an improved Cdk2 inhibition could be achieved by small structural changes. An example from the extensive structure-activity relationship study undertook, is the alanine scan of p21 sequence 149–160 that led to the inhibitor Asp-Phe-Tyr-His-Ala-Lys-Arg-Arg-Leu-Ile-Phe-Ser-$NH_2$. This peptide is a 100 fold more active on Cdk2 cyclin E complex for the phosphorylation of GST-Rb (Zheleva et al., 2002).
– $p16^{INK4}$. The protein p16 is the only member of the INK4/CDKN2 gene products that is linked to tumour suppression. It acts at the level of Cdk-cyclin D interaction, possibly by binding to Cdk4 or in a more complex manner involving another protein (Fåhraeus et al., 1998). A strategy, related to the one described above, led to the preparation of a 20-mer peptide, derived from p16 sequence, which is able to inhibit Cdk4-cyclin D1 kinase *in vitro* and block cell cycle progression through G1 (Fåhraeus et al., 1996). Further studies led to a much smaller peptide (Phe-Leu-Asp-Thr-Leu-Val-Val-Leu-His-Arg) which is still a kinase inhibitor although, contrary to its parent peptides, does not bind to the Cdk4 anymore. Moreover, when linked to the *Antennapedia* carrier sequence, it also stopped cell cycle progression (Fåhraeus et al., 1998).

### *III.4 Inhibitors of E2F/DP and E2F/DNA interactions*

Further down in the signalling cascade involving p16 is the heterodimeric association between the transcription factor E2F and another protein (of the DP family) prior to a binding to DNA. The E2F/DP transcription factor seems to have a role as both a tumour suppressor and an oncogene in mice (Yamasaki, 1999). A two hybrids strategy search was devised and led to aptamer and unconstrained peptidic compounds able to prevent this association (Fabbrizio et al., 1999). Moreover, one of the 20-mer peptide (Arg-Cys-Val-Arg-Cys-Arg-Phe-Val-Val-Trp-Ile-Gly-Leu-Arg-Val-Arg-Cys-Leu-Val) also inhibited E2F function *in vitro*. It is noteworthy that this peptide contains the sequence Trp-Ile-Gly-Leu which corresponds to a highly conserved motif present in the protein DP. Since a previous study (Bandara et al., 1997) showed that a 15-mer peptide containing this sequence had no significant effect – much longer one had – on E2F heterodimerisation, further structural requirement must be involved.

The naturally occurring hexadepsipeptide GE3 (Fig. 6) was found to be cytotoxic on tumour cell lines and, most remarkably, to probably interact with E2F (Sakai et al., 1997). It is noteworthy that many closely related depsipeptides such as azinothricin (Maehr et al., 1986), A83586C (Smitka et al., 1988), variapeptin and citropeptin (Nakagawa et al., 1990), aurantimycins (Gräfe et al., 1995), verucopeptin (Sugawara et al., 1993), polyoxypeptin (Umezawa et al., 1999) and pipalamycin (Uchihata et al., 2002) were also reported for their antitumor potential.

Another original avenue exists as the N-terminal dodecanoate of Leu-Asn-Trp-Ala-Trp-Ala-Ala-Glu-Val-Leu-Lys-Val-Gln-Lys-Arg-Arg-Ile-Tyr-Asp-Ile-Thr-Asn-Val-Leu-Glu-Gly-Ile-Gln-Leu-Ile-Ala-$NH_2$ is interfering with the E2F activity *via* a binding to its DNA recognition domain (Shibata et al., 1998). More recently, a patent claimed the three different short peptides Phe-Trp-Leu-Arg-Phe-Thr or Trp-Val-Arg-Trp-His-Phe and Trp-His-Phe-Ile-Phe-Trp as well

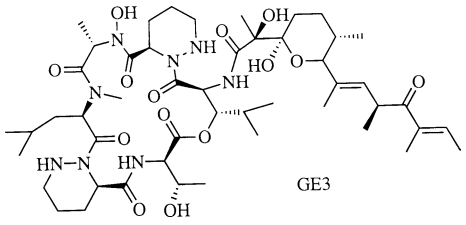



**Fig. 6.** A naturally occurring antagonist of E2F

as the two longer one Ile-Trp-Leu-Ser-Gly-Leu-Ser-Arg-Gly-Val-Trp-Val-Ser-Phe-Pro and Gly-Ser-Arg-Ile-Leu-Thr-Phe-Arg-Ser-Gly-Ser-Trp-Tyr-Ala-Ser as inhibitors of the E2F-DNA interaction and their use against cell proliferation (Muller et al., 2000). Moreover, it is noteworthy that the c-Myc-derived peptide Asp-Glu-Leu-Lys-Arg-Ala-Phe-Ala-Ala-Leu-Arg-Asp-Gln-Ile linked to an *Antennapedia* internalising sequence inhibits cancer cell growth via a similar mechanism (Draeger and Mullen, 1994; Giorello et al., 1998).

### *III.5 Src homology domains 2 and 3 and Bcl homology domain 3*

Src homology 2 domains (SH2) are 100 amino acid-long sequences that bind phosphotyrosine-containing motifs in a sequence-specific manner. These SH2 domains were first found in the src family of cytoplasmic protein-kinases and exist in many adaptor proteins involved in intracellular signal transduction (Helmreich, 2001; Pawson and Schlessinger, 1993). On the other hand, the src homology domain 3 (SH3) are 55–70 amino acid-long sequences, that bind proline-rich peptides, that are also found in many proteins (Pawson and Schlessinger, 1993). Also, some or all of the four different Bcl homology domains (including Bcl homology domain 3 (BH3)) can be found in a still growing family of proteins involved in the regulation of apoptosis (Adams and Cory, 1998; Chao and Korsmeyer, 1998). Amongst the cancer-related signalling proteins, many interact via such domains. Recent reviews describe the potential targets and the compounds found (Sawyer, 1998; Shakespeare, 2001). But for few other cases (Bardelli et al., 1997; Bardelli et al., 1999; Kardinal et al., 2000), three type of proteins (Grb2, Src and Bcl2) are the main anticancer targets of research groups aiming at finding specific inhibitors of their SH2, SH3 or BH3-mediated interaction with other proteins.

– Grb2 (growth factor receptor-bound protein 2) is the most studied example. This is an adaptor protein involved, for example, in the Ras signalling pathway (Garbay et al., 2000). Inside the cell, the signal beginning from a tyrosine kinase receptor which, when phosphorylated, will bind to Grb2 via its SH2 domain. This protein will then bind, via its two SH3 domains, to Sos (son of sevenless) which in turns binds RasGDP. When this system loses some of its control, it leads to a cellular proliferation and differentiation. Thus, as for the interaction between Ras and Raf, inhibition of the tyrosine kinase-Grb2 or the Sos-Grb2 interactions might lead to antitumor agents, provided that the control loss has taken place upstream to the targeted interaction. Important effort have been made to find strong and selective Grb2 SH2-based ligands (Ettmayer et al., 1999; Garbay et al., 2000; Gay et al., 1999; Hart et al., 1999; Liu et al., 2000a; Yao et al., 1999). One of the problem is the apparent necessity to keep a phosphate group to have a strong *ex vivo* affinity although this very phosphate leads to compounds with a poor activity on cellular assays. One way to overcome this problem was to prepare prodrugs of these phosphate-containing compounds (Gay et al., 1999; Liu et al., 2000b). Another, to prepare phosphonate-derived compound such as the pentapeptide depicted in figure 7 which is, remarkably, a tubulogenesis inhibitor (Battistini et al., 1997). In a different approach, phosphorus-free ligands were designed (Fretz et al., 2000; Hart et al., 1999; Yao et al., 1999). In one instance, this last avenue was opened by a peptidic sequence, found by phage display technique (Oligino et al., 1997), and thus unrelated to the known Shc (another adaptor protein) binding motify pTyr-Val-Asn-Val for Grb2 (Comoglio and Ponzetto, 1995). Further synthetic refinement of the lead compound yielded a cyclic structure (Fig. 7), with submicromolar affinity for Grb2 SH2 domain, in which the $\gamma$-carboxyglutamate residue compensates for the lack of phosphate (Long et al., 1999; Lung et al., 2001). It is noteworthy that the same research group is now focusing on Grb7, another adapter-type signalling protein (Han et al., 2001), and has reported the discovery of Grb7 SH2-based peptidic ligands (Pero et al., 2002).

In an other approach, based on X-ray derived structures, very strong Grb2 SH3-based ligands were found

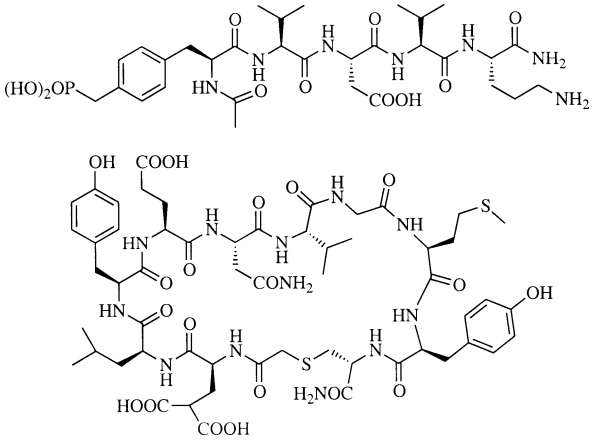


**Fig. 7.** A phosphonated and a phosphorus-free SH2-based ligand of Grb2

(Cussac et al., 1999; Nguyen et al., 1998). Attachment of one of these ligand (the "peptimer" [Val-Pro-Pro-Pro-Val-Pro-Pro-Arg-Arg-Arg]$_2$N$\alpha$,N$\varepsilon$Lys) to the *Antennapedia* cell internalising sequence enable to prove that an inhibition of NIH3T3 colonies formation could be achieved at micromolar concentration (Cussac et al., 1999; Garbay et al., 2000).

– The pp60$^{c\text{-}src}$ (Src) protein is a nonreceptor tyrosine kinase containing an SH2 and an SH3 domain. This protein is associated with breast cancer (Luttrell et al., 1994). Accordingly research groups focused on the design of SH2-based ligand to Src in attempts to block its interaction with the protein involved in subsequent cellular proliferation (Gilmer et al., 1994; Lunney et al., 1997; Plummer et al., 1997; Waksman et al., 1993). Some very simple phosphorylated ligands, such as Ac(p)Tyr-Glu-Glu-Ile-$NH_2$, were found. Again a lack of *in vivo* activity is due to the necessary presence of a phosphate group on the tyrosine residue. This group is either the cause of a poor intracellular penetration or is hydrolysed inside the cell. Hopefully further research will lead to (probably) nonpeptidic analogues which will enable a proof of principle (Buchanan et al., 1999a; Buchanan et al., 1999b; Buchanan et al., 1999c; Pacofsky et al., 1998).
– Bcl2 and related cytoplasmic protein such as Bak, Bax and Bad play a central role in the regulation of apoptosis as "arbiters of cell survival" (Adams and Cory, 1998; Gross et al., 1999). A Bcl2 gene overexpression is observed in a wide number of cancers and this level of expression does correlate with cancer chemotherapeutic or radiation resistances (Huang et al., 2000). As BH3-based heterodimerizations between Bcl2 and the apoptose-promoting proteins Bax, Bak, Bid and Bad were demonstrated (Chao and Korsmeyer, 1998; Diaz et al., 1997; Sattler et al., 1997), this became a target for anticancer research (Huang, 2000). Three different 16-mer peptides, mimicking the BH3 domain of Bax (Lys-Lys-Leu-Ser-Glu-Cys-Leu-Lys-Arg-Ile-Gly-Asp-Glu-Leu-Asp-Ser) Bak (Gly-Gln-Val-Gly-Arg-Gln-Leu-Ala-Ile-Ile-Gly-Asp-Asp-Ile-Asn-Arg) or Bid (Arg-Asn-Ile-Ala-Arg-His-Leu-Ala-Gln-Val-Gly-Asp-Ser-Met-Asp-Arg), were shown to bind the antiapoptotic Bcl2 and trigger apoptosis in a cell-free system (Cosulich et al., 1997). A peptide made of an *Antennapedia* internalisation sequence and a segment of Bak was proven to trigger apoptosis (Holinger et al., 1999). Moreover, a second proof of principle was achieved with a Bad-derived 25-mer peptide (Lys-Asn-Leu-Trp-Ala-Ala-Gln-Arg-Tyr-Gly-Arg-Glu-Leu-Arg-Arg-Met-Ser-Asp-Glu-Phe-Glu-Gly-Ser-Phe-Lys-Gly-Leu) which was acetylated with decanoic acid to increase its cell-membrane permeability. The pertinence of the target was then established on animal as mice, treated with this modified peptide, survived much longer than untreated mice (Wang et al., 2000). Interestingly a similar approach was undertaken and an "Antennapedia-derived" Bad 21-mer was shown to cause apoptosis but, independently of the Bcl-2 pathway (Schimmer et al., 2001). Current investigations still focus on peptides mimicking the BH3 domain of Bak (Finnegan et al., 2001) as well as on non-peptidic molecules binding the BH3 domain of Bcl2 (Enyedy et al., 2001).

### *III.6 Cell adhesion proteins binding agents, antimetastatics/antiangiogenics*

This part concerns cell adhesion inhibitors that alter the properties of extracellular matrix proteins which play a central role in metastasis and angiogenesis. Cell adhesion proteins can specifically bind to peptidic motifs such as Arg-Gly-Asp (RGD) or Tyr-Ile-Gly-Ser-Arg (YIGSR) or other so far less defined. These are actually the anchoring zones of all the proteins involved in cellular adhesion (i.e.: thrombin B-chain or fibronectin contain this RGD sequence and YIGSR is found in laminin B1 chain). Many ligands analogues of the peptidic RGD or YIGSR motifs were made

(D'Souza et al., 1991) and their antimetastatic effect measured, as it was recognised (Humphries et al., 1986; Iwamoto et al., 1987; Terranova et al., 1984) that they were the underlying bases for cellular migration or metastasis. Further work on RGD-based peptides pointed out the importance to, out of the many integrins existing (Hynes, 1992), focus on selective antagonists for the $\alpha_v\beta_3$ integrin (Brooks et al., 1994; Haubner et al., 1987; Montgomery et al., 1994; Ruoslahti and Reed, 1994). Mentioning all the peptidic analogues would be beyond the scope of this review (Craig et al., 1995). One of the achievement of this avenue of research is the cyclic pentapeptide cilengitide (Fig. 8) which is currently undergoing clinical studies as an antiangiogenic drug (Dechantsreiter et al., 1999; Sorbera et al., 2001). Moreover, one recent report mentions the interesting fact that RGD-derived peptides may also induce apoptosis via a direct caspase-3 activation (Buckley et al., 1999). The clinical efficacy of $\alpha_v\beta_3$ antagonists (peptidic or not) is today the last step remaining to be demonstrated for this antitumor approach (Coleman and Le, 2002).

Comparatively less work was done on the laminin binding site Tyr-Ile-Gly-Ser-Arg, maybe because of its longer length. Here is a list of compounds made which illustrates some of the efforts deployed to transform such motif into a usable drug: Cys-Asp-Pro-Gly-Tyr-Ile-Gly-Ser-Arg-$NH_2$ (Martin et al., 1989); Ac-Tyr-Ile-Gly-Ser-Arg-$NH_2$ (Schasteen, 1991); Ac-Tyr-Ile-Gly-Ser-Arg-$NHCH_3$ (McKelvey et al., 1991); Ac-Tyr-Ile-Gly-Ser-Arg-$N(CH_3)_2$ (Mori et al., 1994); Phe(p$NH_2$)-Ile-Gly-Ser-Arg-$NH_2$ (Zhao et al., 1994); Ac-Tyr-Ile-Gly-Ser-Arg-$NHCH(CH_3)_2$ (Mori et al., 1995b); $CO$(Asp-Tyr-Ile-Gly-Ser-Arg-$NHPr)_2$ (Mori et al., 1995a).

Other peptides, with sequences differing from RGD or YIGSR were also found to be antimetastatic. A recent paper describes efforts to find such sequence that led for instance to the disulfide-bridged Gys-Trp-Asp-Asp-Gly-Trp-Leu-Cys, via a phage display library (Pasqualini et al., 1995).

The laminin receptor-derived compound Ile-Pro-Cys-Asn-Asn-Lys-Gly-Ala-His-Ser-Val-Gly-Leu-Met-Trp-Trp-Met-Leu-Ala-Arg was reported to inhibit cancer cell attachment to endothelium (Castronovo et al., 1991; Magnifico et al., 1996). Moreover, as a study demonstrated that there are many peptide fragments of laminin that have an affinity for cells, it is likely that some new antimetastatic targets may be better defined in the future (Nomizu et al., 1997).

The tumstatin fragment Gln-Arg-Phe-Thr-Thr-Met-Pro-Phe-Leu-Phe-Cys-Asn-Val-Asn-Asp-Val-Cys-Asn-Phe and longer one containing this sequence are binding $\alpha_v\beta_3$ integrin and have an antiangiogenic potential (Maeshima et al., 2001).

Another phage display-based search, focusing on angiogenic vessels, led to the pentadecapeptide Ala-Ser-Ser-Ser-Tyr-Pro-Leu-Ile-His-Trp-Arg-Pro-Trp-Ala-Arg, which significantly suppress tumour growth. A noteworthy features is that fragment peptides containing the motif Trp-Arg-Pro retained some activity (Asai et al., 2002).

*Thrombospondin-1 mimics.* Peptides and analogues bearing the type I repeat (Lys-Arg-Phe-Lys-Gln-Asp-Gly-Gly-Trp-Ser-His-Trp-Ser-Pro-Trp-Ser-Ser-Cys) of the extracellular matrix glycoprotein thrombospondin-1, which is involved in antiangiogenesis, have been reported for antiproliferative and antitumor activities (Guo et al., 1997). Further research, based on D-amino acid substitutions, notably led to the heptapeptide Ac-Gly-Val-D-Ile-Thr-Arg-Ile-Arg-NHEt which also corresponds to a segment of the type I repeat sequence but one following the 18-mer described above (Dawson et al., 1999). Moreover, the sequence Ac-Gly-Val-D-Ile-Thr-Nva-Ile-Arg-Pro-NHEt was reported for its antitumor properties (Reiher et al., 2002) and related peptides such as Ac-Sar-Gly-Lys(Ac)-D-Leu-Thr-Nva-Ile-Arg-Pro-NHEt and Ac-Sar-Gly-Val-D-Ile-Thr-NMeNva-Ile-Arg-Pro-NHEt were patented (Haviv et al., 2001a; Haviv et al., 2001b).

*Angiostatin analogues.* Following the discovery of angiostatin, a naturally occurring fragment of plasminogen, some of its kringes domains were demonstrated to be important (Cao et al., 1997; Cao et al., 1996). However, much shorter peptides, derived from the kringle domains or present in the sequence of endostatin, were found quite active and were patented. The following peptides, "bracketed" by prolines residues, are amongst the noteworthy compounds: Ser-Pro-His-Arg-Pro-Arg-Phe-Ser-Pro-Ala; Ser-Pro-His-Ala-His-Gly-Tyr-Ile-Pro-Ser and Thr-Pro-His-Thr-His-Asn-Arg-Thr-Pro-Glu or Thr-Pro-His-Arg-His-Gln-Lys-Thr-Pro-Glu and Glu-Pro-His-Arg-His-Ser-Ile-Phe-Thr-Pro-Glu (Ge and Kini, 2001). These prolines residues may actually provide an inherent structural requirement since such residues are quite frequently found near motifs responsible

for a protein-protein interaction (Kini and Evans, 1995).

*Cadherins His-Ala-Val – derived motifs.* Short cyclic peptides, containing the highly conserved cadherins motif His-Ala-Val, such as Ac-Cys-His-Ala-Val-Cys-$NH_2$ were recently patented for their angiogenis inhibition potential (Blaschuk et al., 2002). This work probably opens a new avenue for this approach as cadherins are calcium-binding membrane proteins enabling cell processes such as segregation and regulation (Williams et al., 2000).

It is quite possible that the mechanism of action of some of the following peptides, reported for their antimetastatic potential, has nothing to do with an interaction with extra cellular matrix proteins: a fragment of the high mobility group 17 Ala-Glu-Asp-Gly-Asp-Ala-Lys-Thr-Asp-Glu-Ala-Gln-Lys-Ala-Glu-Gly-Ala-Gly-Asp-Ala-Lys (Akedo et al., 1991; Isoai et al., 1992); analogues of Glu-Ile-Leu-Asp-Val containing D amino-acids (Kaneda et al., 1997) or polyethyleneglycol derivatives of such motif (Kawasaki et al., 1996); kininogen L fragments and peptides containing Trp-Gly-His-Glu-Lys-Gln-Arg or Lys-Gly-Lys-Lys-Asn-Gly-Lys-His (Matsuda et al., 1996); thrombin fragment Tyr-Pro-Pro-Trp-Asn-Lys-Asn-Phe-Thr-Glu-Asn-Asp-Leu-Leu or shorter one (Packard, 1987). Moreover, a quite simple tripeptide (Fig. 8), of natural origin, was claimed to have a metastasis suppressing activity (Terano et al., 1986).

### *III.7 Antimitotic peptides, tubulin or actin interfering compounds*

Microtubules and actin filaments are the cytoskeletal protein polymers involved in cell growth and division. The polymerisation of $\alpha\beta$-tubulin dimers in microtubules is the target of many important antitumor drugs. It is the drug-induced alteration of tubulin polymerisation or depolymerisation dynamics which is hampering the correct occurrence of microtubules and is the underlying mechanism of the antitumor action (Correia, 1991; Jordan and Wilson, 1998). Moreover, other compounds owe their cytotoxicity to the disorganisation of actin filaments that are made from the polymerisation of actin monomers. We chose to class these two types of compounds as inhibitors of protein-protein interactions albeit they are multimeric interactions in the present cases. In the following are actually listed a great number of antimitotics of natural origin (Hamel, 1992; von Angerer, 2000).

*III.7.1 Tubulin-interacting peptides.* The weakly cytotoxic phomopsin A (Fig. 9) is isolated from the fungus *Phomopsis leptostromiformi* and act at the level of tubulin (Hamel, 1992; Lacey et al., 1987). It is noteworthy that the related ustiloxins A–D (Fig. 9) were extracted from the pathogen *Ustilaginoidea virens* and are also inhibitors of tubulin polymerisation (Li et al., 1995b; Ludueña et al., 1994).

The discovery of the cytotoxic 16-membered cyclic epoxyde-containing cryptophycins was reviewed recently (Corbett et al., 1997). They were isolated from blue-green algae and found to be antimitotic and act on tubulin functions (Mooberry et al., 1996; Moore et al., 1996; Smith and Zhang, 1996). A review of analogues of this structure has been published (Moore et al., 1996) and more compounds have been reported since (Georg et al., 1998; Norman and Shih, 1998; Patel et al., 1999; Patel et al., 1998; Shih et al., 1999; Shih and Williams, 1998; White et al., 1999). The arenastatins (Fig. 10), which have very similar structure, were isolated from the marine sponge Dysidea arenaria and were also leads for structure-activity studies (Kitagawa and Kobayashi, 1996; Kobayashi et al., 1994b; Kobayashi et al., 1995). The hindered synthetic dimethyl analogue cryptophycin 52 (Fig. 10) was found more stable toward hydrolysis and is the main candidate for a clinical development (Eggen and Georg, 2002).

A series of cytotoxic tryptophan-derived compounds have been identified so far in four sponge

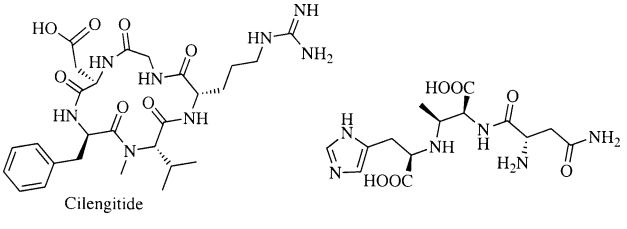



**Fig. 8.** Cilengitide and a naturally occurring metastasis inhibitor

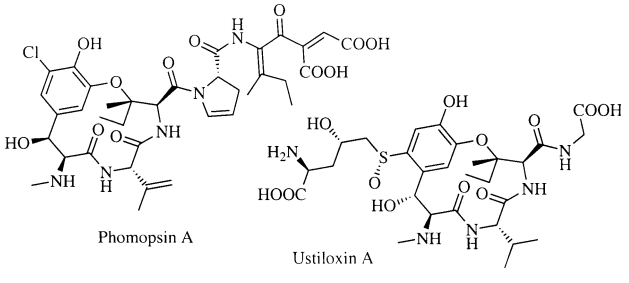



**Fig. 9.** Structures of phomopsin A and ustiloxin A

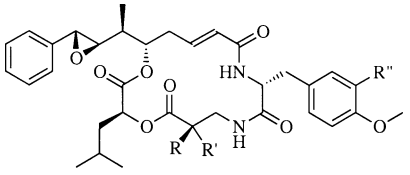



**Fig. 10.** Structures of cryptophycin 52 and arenastatin A

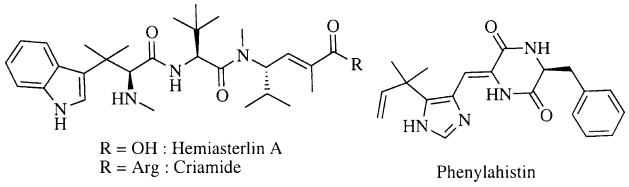



**Fig. 11.** Hemiasterlin A, criamide and phenylahistin

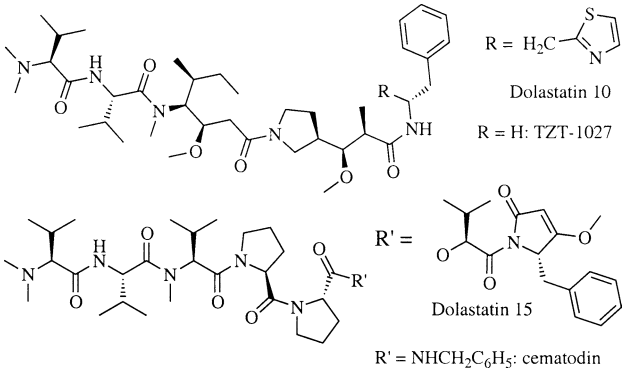



**Fig. 12.** Dolastatin 10 and 15 and two analogues

genera (Gamble et al., 1999). Hemiasterlin A (Fig. 11) was isolated from Hemiasterella minor and, along with arginine amides criamide A, from *Cymbastela* (Andersen et al., 1997; Coleman et al., 1995; Talpir et al., 1994) and was found to act via inhibition of microtubule dynamics (Anderson et al., 1997; Bai et al., 1999). It is noteworthy that the more rigid milnamide, which has a tetrahydropyridoindole ("Tpi"; see Fig. 2) instead of the trimethyltryptophan moiety of hemiasterlin, is also cytotoxic (Crews et al., 1994). Moreover an analogue in which this indole is replaced by a phenyl is more active than the hemiasterlins (Andersen et al., 1999).

Phenylahistin (Fig. 11), which is barely a peptide, is a cytotoxic ketopiperazine derivative (Hayashi et al., 2000; Kanoh et al., 1999a; Kanoh et al., 1999c) that also inhibits tubulin polymerisation (Kanoh et al., 1999b). A remarkable number of other ketopiperazine derivatives such as tryprostatins (Cui et al., 1996a; Cui et al., 1995; Cui et al., 1996b; Cui et al., 1996c) have been reported for their cell cycle inhibition properties and were subsequently shown to inhibit microtubule assembly (Sanz-Cervera et al., 2000; Usui et al., 1998; Zhao et al., 2002). One can wonder at the mechanism of action of the many related compounds (Graz et al., 2000; Milne et al., 1998; Schiavi et al., 2002).

Two reviews report the nearly 25 year-long story of the isolation, identification and synthesis of the many cytotoxic substances found in the sea here *Dolabella* and named dolastatins (Pettit, 1997; Poncet, 1999). Actually, most of these metabolites are probably originated in the cyanobacteria, such as Symploca, that this herbivorous sea hare ingests (Luesch et al., 2001a). Among them, the linear peptides dolastatin 10 (Pettit et al., 1987) and dolastatin 15 (Pettit et al., 1989a) were found to act on tubulin polymerisation. Their structures led to the synthesis of cematodin (de Arruda et al., 1995; Jordan et al., 1998) and TZT-1027 (Kobayashi et al., 1997) which are today, along with dolastatin 10, at different stages of clinical development (Madden et al., 2000; McElroy Jr. et al., 1997; Supko et al., 2000; Vaishampayan et al., 2000; Villalona-Calero et al., 1998). The naturally occurring linear peptides dolastatin C (Sone et al., 1993b), dolastatin H and isodolastatin H (Sone et al., 1996) also displays an N-terminal dimethylamine group. Moreover, the quite unrelated cytotoxic dolastatin 18 (Pettit et al., 1997b) or virenamide C (Carroll et al., 1996b) displays the same C-terminal thiooxazole-containing amide as dolastatin 10. These naturally originated compounds, the more recently isolated methyl homologue of dolastatin 10, symplostatin 1 (Luesch et al., 2001a) and the analogues synthesised, provide fascinating structure-activity relationships which were reviewed recently (Pettit et al., 1998a; Poncet, 1999).

Bicyclic peptides with structures bearing a central indole moiety such as moroidin and celogentin were reported for their tubulin polymerisation inhibition (Kobayashi et al., 2001; Morita et al., 2000). As a conclusion to this section, we should mention the recently isolated tubulysins which will probably be at the source of important structure-activity studies (Hoefle et al., 2002; Sasse et al., 2000). Tubulysin D (Fig. 13) displays a picomolar activity on mammalian cell lines and induces a complete disappearance of the cellular microtubules. One of the remarkable feature of these compounds (apart from a N-terminal tertiary amine

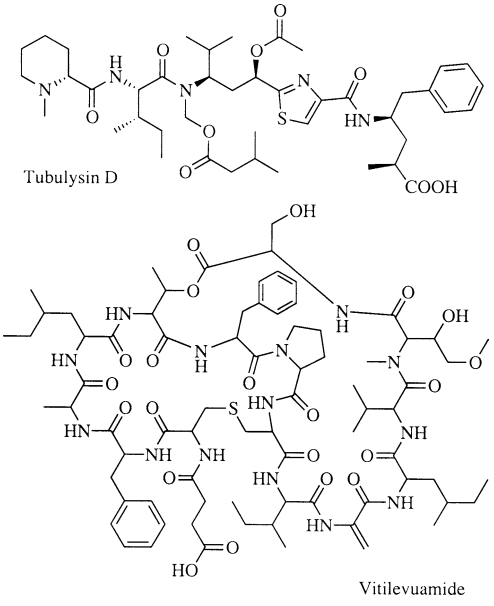



**Fig. 13.** Tubulysin D and vitilevuamide

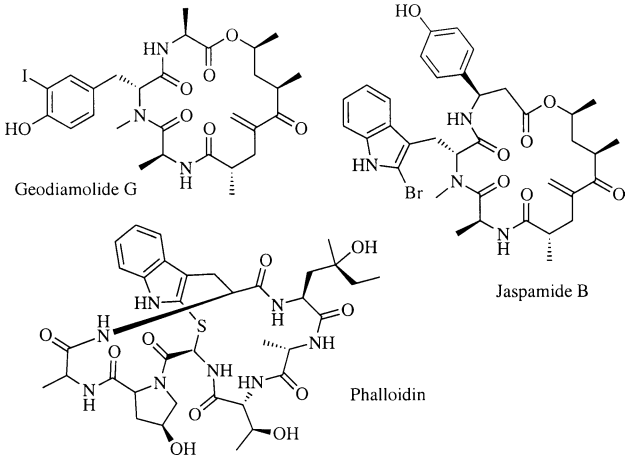


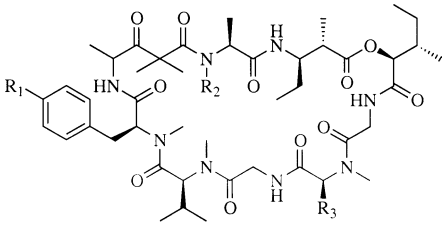

**Fig. 14.** Geodiamolide G, jaspamide B and phalloidin

reminiscent of dolastatin 15 analogues (Janssen et al., 1998)) is an acyloxymethyl side chain that could make them actual lipophilic prodrugs, substrates of an *in vivo* hydrolysis. Even more recently, the remarkable bicyclic depsipeptide vitilevuamide (Fig. 13) was isolated from the ascidians Didemnum cuculliferum and Polysyncranton lithostrotum. The cytotoxicity of this compound is at least partly due to the inhibition of tubulin polymerisation via an interaction at a different site from the binding site of colchicine, the *vinca* alkaloids or dolastatin 10 (Edler et al., 2002).

*III.7.2 Actin-interacting peptides.* Jasplakinolide (Crews et al., 1986)/jaspamides (Zabriskie et al., 1986; Zampella et al., 1999) and chrondamide D are related cytotoxic peptides (Breakman et al., 1987; Crews et al., 1994) that disrupt the proper function of actin (Bubb et al., 1994; Bubb et al., 2000). As depicted on Fig. 14, it is tempting to relate the jasplakinolide/jaspamides to the cytotoxic geodiamolides (Chan et al., 1987; Coleman et al., 1995; Coleman et al., 1999; de Silva et al., 1990). These compounds all display a 12-carbon polypropionate unit. Interestingly, the more structurally different doliculide also bears a iodotyrosine residue as the geodiamolides (Ishiwata et al., 1994a; Ishiwata et al., 1994b; Ishiwata et al., 1994c) and was recently reported to enhance actin assembly (Bai et al., 2002).

The phallotoxins, such as phalloidin (Fig. 14) are toxic peptides isolated from the poisonous mushroom *Amanita phalloides* (Wieland, 1968) that also interact with actin by preventing the depolymerisation of F-actin into G-actin (Miyamoto et al., 1986; Wieland, 1987). The noteworthy 4-hydroxyproline residue was actually found to be essential (Wieland and Faulstich, 1978). Remarkably, the amatoxins which are related to the phallotoxins, are "only" weak inhibitors of RNA polymerase B (Wieland and Faulstich, 1978). A structural common point for an affinity for actin and the inhibition of RNA polymerase remain to be described. This is actually reminiscent of the (non peptidic) etoposides analogues in which some compounds are inhibitors of topoisomerase II function while others are interfering with tubulin. The unrelated antitumor peptidic derivatives cupolamide A and astins, for which no mechanism of action has been suggested, also feature, respectively, a functionnalised 4-sulfated or 3,4-bischlorinated proline residues (Bonnington et al., 1997; Morita et al., 1993; Morita et al., 1996c). Moreover 4-hydroxyproline-containing di and tripeptides have been reported for their cytotoxicity (Hall and Chen, 1999).

The total synthesis of dolastatin 11 allowed the elucidation of its mechanism of action (Bates et al., 1997). This compound, and (Fig. 15) the structurally related majusculamide C (Carter et al., 1984), lyngbyastatin and dolastatin 12 (Harrigan et al., 1998; Luesch et al., 1999), act on the cellular actin filament network and it was shown that dolastatin 11 induces hyperpolymerisation of purified actin. Dolastatin 11 is the most cytotoxic of the peptides/depsipeptides that induces the assembly of actin *in vitro* (Bai et al., 2001). However, pharmaceutical development of this class of



Dolastatin 11: $R_1$ = OMe, $R_2$ = H, $R_3$ = $CH_2iPr$
Dolastatin 12: $R_1$ = H, $R_2$ = $CH_3$, $R_3$ = $CH_2iPr$
Lyngbyastatin 1: $R_1$ = OMe, $R_2$ = $CH_3$, $R_3$ = $CH_2iPr$
Majusculamide C: $R_1$ = OMe, $R_2$ = H, $R_3$ = (*S*) $CHsBu$

**Fig. 15.** Dolastatin 11 and related substances

compound may be discontinued as a pulmonary toxicity was found for jasplakinolide (Bai et al., 2001; Schindler-Horvat et al., 1998).

### *III.8 Less investigated examples*

*III.8.1 Ras-Raf interaction.* The activated Raf kinases are the key to a typical cellular signalling pathway to, for instance, cell proliferation via mitogen-activated protein kinases (Helmreich, 2001). Activation of Raf kinase has been shown to be controlled by the interaction with the membrane-translocated protein Ras. Ex vivo inhibition of protein Ras and protein Raf interaction has been achieved by peptides sequences found in either Ras or Raf (Barnard et al., 1998; Niehof et al., 1995; Ohnishi et al., 1998). However, even for the short Raf-derived peptide Cys-Cys-Val-Ala-Phe-Arg-Leu, no *in vivo* efficiency of such compound could be demonstrated (Barnard et al., 1998).

*III.8.2 Human papillomavirus oncoprotein E6 and E7.* Human papillomavirus-associated carcinogenesis is linked to the coexpression of the two viral proteins E6 and E7 in the infected cells. As protein E7 was demonstrated to bind to the retinoblastoma protein, an inhibitor to this interaction could lead to an original therapy for papillomavirus-originated cancer. While a review (Huber et al., 1994) describes the very extensive efforts made to finds such a peptide, it is only in a recent article that the hexapeptide Leu-Phe-Tyr-Lys-Lys-Val, actually corresponding to a fragment of the retinoblastoma protein, was reported to be cytotoxic against neoplastic cells containing protein E7 (Radulescu and Jacques, 2000). On the other hand, the E6 protein interacts with the p53 protein resulting in its ubiquitin-dependant degradation. Again, after an unsuccessful attempt to find short peptides (Huber et al., 1994), another approach led to many 20 amino acids-long peptidic aptamers that binds E6. These peptides were found to cause the exclusive apoptotic elimination of the E6-bearing cancer cells (Butz et al., 2000).

*III.8.3 Inhibition of mammalian ribonucleotide reductase assembly.* Mammalian ribonucleotide reductase is a target for antitumor treatment (Szekeres et al., 1997). A new avenue could exist in peptide-based inhibitors as it was shown that a small compound (AcPhe-Thr-Leu-Asp-Ala-Asp-Phe) corresponding to the C-terminus of R2 subunit of ribonucleotide reductase does inhibit its assembly with the R1 subunit (Fisher et al., 1993). More recent work led to a series of lactam-bridged compounds with even better inhibitory effect (Liehr et al., 1999).

*III.8.4 Restauration of Fas-induced apoptosis.* An article describes derivatives of the tripeptide Ser-Leu-Val which are able to inhibit an association between Fas, a cell surface receptor, and FAP-1 a protein which is involved in acquisition of a resistance against anti-Fas antibody-mediated apoptosis. Thus such peptide may have the potential to restore the function of Fas (Sawa et al., 1999).

## IV Enzymes inhibitors

### *IV.1 Ras farnesyl transferase*

The antitumor potential of such inhibitors is due to the blocking of the carboxy-terminal cysteine prenylation of protein Ras. This prevents its anchorage to the inner side of cell membrane, which is crucial for the cell multiplication signals transmission (Crul et al., 2001). The first cysteine farnesyl transferase inhibitors found were based on the carboxy terminal part of protein Ras. Many peptides mimicking the last four amino acids of Ras with the general formula Cys-A-A-X are thus inhibiting the farnesyl transferase (Perrin et al., 1996). The thiol-free compound depicted on figure 16, is also derived from this CAAX motif and illustrates the intensive structure-activity studies undertaken (Anthony et al., 1996). All these compounds, including the fact that some entered clinical trials, were reviewed (Crul et al., 2001; Leonard and Sebolt-Leopold, 1999; Omer and Kohl, 1997; Perrin et al., 1996; Sebti and Hamilton, 1997). We should mention a second class of peptidic inhibitors (Fig. 16) which were found using peptide libraries. Their mechanism of action, as for other non peptidic compounds found (Aoyama et al., 1998), is based on an interference with

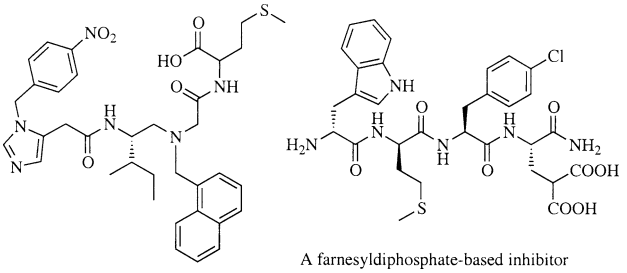



**Fig. 16.** Example of the two peptidic class of farnesyl transferase inhibitors

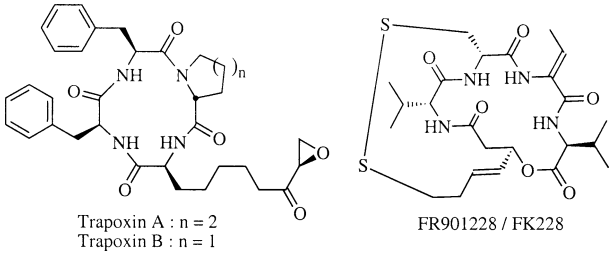



**Fig. 17.** Structures of trapoxins A, B and R901228 / FK228

the farnesyldiphosphate binding site (Bogusky et al., 1999).

### *IV.2 Histone deacetylation*

Histone deacetylase catalyses the removal of acetyl group from the $\varepsilon$-amine of lysine residues present near the amino terminus of nucleosomal histones. Inhibition of this process was shown to be a target for cytotoxic compounds, possibly by the prevention of DNA unwinding from around the histone prior to its transcription (Yoshida et al., 2001). Recent studies point out a much more elaborate role for post-translational modification of histones that would be hindered by deacetylation inhibitors (Strahl and Allis, 2000). Moreover, the histone deacetylase inhibitors effect on the up-regulation of $p21^{WAF1/CIP1}$ was investigated (Burgess et al., 2001).

The two tetrapeptides trapoxins A and B (Fig. 17), containing an epoxyde moiety, were isolated from *Helicoma ambiens* (Itazaki et al., 1990). They are related to the many epoxyde-containing cyclic tetrapeptides known such as Cyl-2 (Hirota et al., 1973), chlamydocin (von Closse and Huguenin, 1974), HC-toxin (Liesch et al., 1982) and WF-3161 (Umehara et al., 1983). They were found to display detransforming activity against *v-sis* oncogene transformed NIH3T3 cells (Itazaki et al., 1990). The first structure-activity studies aiming at improving the poor stability of these compounds showed that the chemically reactive epoxyde moiety could be replaced with other functions, reactive as well (Bernadi et al., 1993; Shute et al., 1987). More recently, analogues, based on trapoxin B structure, not only pointed out the importance of the D-amino acids chirality but also confirmed (Tomizaki et al., 1999) that such compound have a capacity for histone deacetylase inhibition (Kijima et al., 1993; Taunton et al., 1996). Recent work showed that the keto-epoxyde group could be replaced by a hydroxamate function (Komatsu et al., 2001; Yoshida et al., 2001). The related cyclic peptide such as apicidin (Singh et al., 1996) and diheteropeptin (Masuoka et al., 2000) display somewhat less reactive side chains (an N-methoxy indole or a diol) and retain biological activities. Moreover, a recent patent describes very active compounds only bearing an $\alpha$-hydroxy ketone-containing side chain (Mori et al., 2000).

The antitumor peptide FR901228 (or FK 228) (Fig. 17) was isolated from *Chromobacterium violaceum* (Ueda et al., 1994a; Ueda et al., 1994b) and was later found to be also an inhibitor of histone deacetylase (Nakajima et al., 1998). Its pharmacological (Chan et al., 1997) and antiangiogenic (Kwon et al., 2002) properties made it a good candidate for clinical development (Piekarz et al., 2001). It is noteworthy that the less functionnalised spiruchostatins were reported for a gene expression enhancement (Masuoka et al., 2001). Hopefully, analogue synthesis will enlighten the structure-activity relationship of this type of compounds that seem to have an effect on cellular signalling pathways (Yu et al., 2002).

Moreover, lunasin a remarkable soybean-extracted 43-mer peptide, or fragments as short as the 17-mer Cys-Glu-Lys-His-Ile-Met-Glu-Lys-Ile-Gln-Gly-Arg-Gly-Asp-Asp-Asp-Asp, were recently found to bind deacetylated histones and thus block cell proliferation by preventing their acetylation (Galvez, 2002; Galvez et al., 2001).

### *IV.3 Inhibitors of proteasome*

The proteasome is an intracellular proteolytic system which displays the peptidase profile of chymotrypsin, trypsin and peptidylglutamyl-peptide protease. This system, in conjunction with ubiquitin, controls the level of many proteins involved in cell proliferation

(see above the case of p53). Potent inhibitors were isolated or prepared such as lactacystin (Fig. 18) (Corey and Wei-Dong, 1999; Omura et al., 1991a; Omura et al., 1991b), epoxyde-containing peptides (Elofson et al., 1999; Koguchi et al., 2000; Sin et al., 1999), the remarkable belactosin A (Fig. 18) or corresponding lipophilic prodrugs (Asai et al., 2000; Yamaguchi et al., 2000) and boron-derived peptides such as PS-341 (Fig. 18) (Adams et al., 1999). From the much more complicated structure of TMC-95A (Kohno et al., 2000), simpler compounds were recently reported to retain an inhibitory action (Kaiser et al., 2002). These inhibitors actually make remarkable tools to elucidate apoptotic processes (Delic et al., 1998; Gazos Lopes et al., 1997; You et al., 1999). Moreover, PS-341 is currently undergoing preclinical investigations (Teicher et al., 1999).

### *IV.4 Protein phosphatases*

Interest in protein phosphatases inhibitor research (Sheppeck et al., 1997) for anticancer treatment could have been renewed by the fact that the strongly cytotoxic naturally-occurring motuporin (Fig. 19) was found to be one of the most potent inhibitor of protein phosphatase 1 (de Silva et al., 1992). The substituted phenyldecadienoic acid chain is also found in other naturally occurring phosphatase inhibiting peptides such as nodularin and microcystins (Goldberg et al., 1995; Namikoshi et al., 1992). This led to structure-activity investigations which showed that the dehydrobutyryl residue of motuporin was, surprisingly (Goldberg et al., 1995), non essential (Samy et al., 1999). More synthetic work was done on microcystin in order to improve the selectivity of its protein phosphatase inhibition (Aggen et al., 1999).

### *IV.5 Ribosome interacting compounds*

Two classes of ribosome-interacting compounds have been extensively studied.

- The antitumor properties of the many derivatives isolated from *Rubia akane*, such as RA-VII, and the related bouvardin (Fig. 20), were reviewed (Itokawa and Takeya, 1993). Their main mechanism of action was shown to be an inhibition of protein synthesis *via* a binding to eukaryotic ribosomes (Sirdeshpande and Toogood, 1995; Zalacain et al., 1982). However an effect on cyclin D1 protein level was reported recently for RA-VII (Wakita et al., 2001). Current research are focused on, for example, hemisynthetic dialkylaminated derivatives which display a higher water solubility (Hitotsuyanagi et al., 1997).
- The highly cytotoxic didemnins derivatives A-E, characterised by a 25-membered cyclic peptide, were found in the marine ascidian *Didemnum molle* (Rinehart Jr. et al., 1981a; Rinehart Jr. et al., 1981b; Rinehart Jr. et al., 1988; Toske and Fenical, 1995). This discovery was followed by much structure activity studies (Jouin et al., 1991) that were reviewed (Schmidt et al., 1999; Vera and Joullié, 2002). The isolation of the related cytotoxic

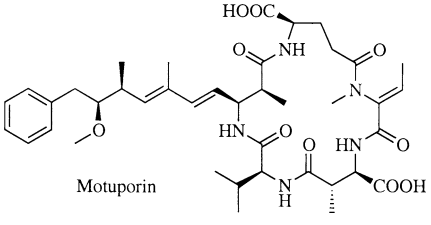



**Fig. 19.** Structure of motuporin

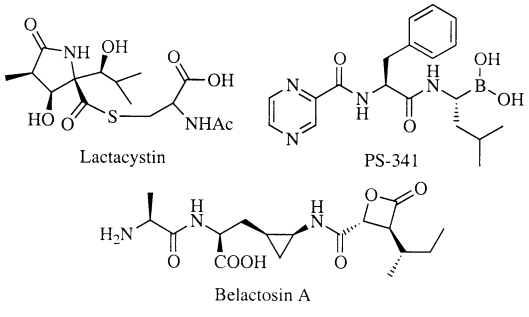



**Fig. 18.** Structures of lactacystin, PS-341 and belactosin A

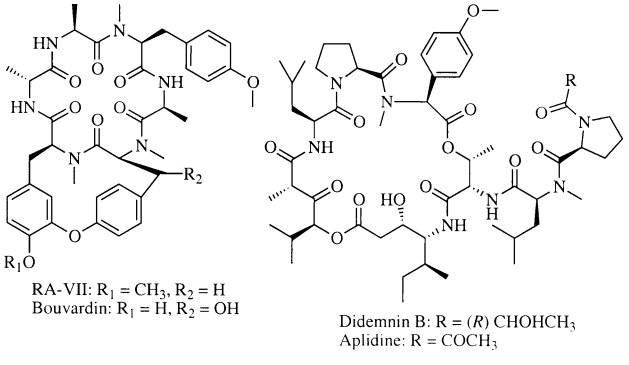



**Fig. 20.** Structure of bouvardin, RA-VII and didemnin B

peptides tamandarins were recently reported (Vervoort and Fenical, 2000). The mechanism of action of didemnins was shown to be based on the inhibition of protein synthesis (Ahuja et al., 2000). Concerning didemnin B, if the preclinical result were encouraging (Jiang et al., 1983), the poor results obtained in the course of phase II trials of didemnin B (Fig. 20) do not warrant any further clinical development of this compound (Hochster et al., 1999; Maroun et al., 1998; Mittelman et al., 1999; Sondak et al., 1994; Taylor et al., 1999). On the other hand, aplidine is still undergoing clinical trials (Jimeno, 2002; Nuijen et al., 1999; Raymond et al., 2000).

### *IV.6 Less investigated examples*

*IV.6.1 Inhibitors of proteases.* There are four major classes of protease enzymes (aspartic, serine, cysteine and metallo) and peptidic inhibitors for these enzymes have been the subject of much research (Leung et al., 2000). On the oncology point of view, urokinase form of plasminogen activator (uPA), cathepsin B and D and various metalloproteases are involved in the metastasis process (Duffy, 1992).

Many non peptidic inhibitors of metalloproteases were found and some are undergoing clinical trials (Brown, 1999; De et al., 1999; Johnson et al., 1998; Whittaker et al., 1999). Recent work describes a phage display-based research which led to the disulfide-bridged cyclic Cys-Thr-Thr-His-Trp-Gly-Phe-Thr-Leu-Cys, a specific inhibitor of the matrix metalloproteinase 2 (gelatinase A) (Koivunen et al., 1999; Medina et al., 2001).

A typical example of the problematic encountered with the other proteases could be the *Actinomycetes*-extracted tripeptide aldehyde leupeptin (Ac-Leu-Leu-ArgCHO) which is an inhibitor of carcinogenesis (Hozumi et al., 1972). This compound was shown to be a good inhibitor of various peptidases such as the serine proteases trypsin, plasmin and papain; the cysteine protease cathepsin B and the aspartic protease cathepsin D (Aoyagi et al., 1977). However even if all these proteases are potential anticancer targets, one of the remaining problem is obtaining a more selective inhibition, for example between serine and cysteine proteases (Leung et al., 2000).

- Recent studies focus on finding specific inhibitors of the serine protease uPA and the mechanism-based peptidic inhibitors were reviewed recently (Tamura et al., 2000). Moreover, a recent article describes the synthesis of peptidic derivatives aiming at the inhibition of the serine protease plasmin (Abato et al., 2002).
- Many irreversible inhibitors of cysteine protease were also reviewed recently (Otto and Schirmeister, 1997). Inhibition of the cysteine protease, involved in the conversion of interleukin-1$\beta$, could be beneficial in tumour treatment (Watanabe et al., 1998). Moreover, the peptidic derivative Z-Phe-Gly-NHO-Bz is an inhibitor of the cysteine protease cathepsins and induces apoptosis in human cancer cells (Zhu and Uckun, 2000).
- Relatively few inhibitors of the lysosomal aspartic protease cathepsin D have been synthesised and studied for their antitumor potential (Bessodes et al., 1999). A recent review describes a possible role for this protease as it is, unexpectedly, regulated by estrogens in breast cancer cell lines (Rochefort and Liaudet-Coopman, 1999).

*IV.6.2 Glyoxalase inhibitors.* Glyoxalase inhibitors research has been quite important and was reviewed (Creigthon et al., 2000). However, a recent report does question the viability of glyoxalase as an anticancer target (Tew, 2000). Few peptides, derived from glutathione, were reported for their inhibition properties of glyoxalase (Kavarana et al., 1999; Vince et al., 1999).

## V Nucleic acid-interacting agents

A nucleic acid interaction does not reflect the mechanism of action of these compounds past the fact that they have an affinity for DNA (or RNA). This binding is followed by other events such as chemical destruction of the DNA strand or inhibition of some of the enzymes involved in DNA chemistry (*i.e.*: maintenance and duplication) such as topoisomerases or polymerases. It is likely that some of the inhibitors of E2F/DNA interaction mentioned above could have been placed in this section.

### *V.1 Bleomycins and actinomycin D*

Bleomycins and actinomycin D are highly active DNA-interacting compounds that are used in cancer chemotherapy (Larsen, 1996). Bleomycin A2, the main component of the bleomycins mixture used, is

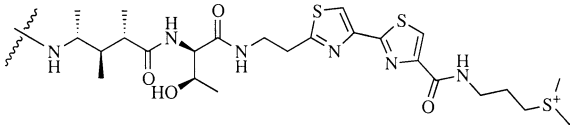


**Fig. 21.** Bleomycin A2 side chain

isolated from *Streptomyces verticillus*. It is a complex molecule made of a diholoside side chain, a metal chelating central part and a bisthiazole-containing peptidic chain (Fig. 21). The latter is responsible for the interaction with DNA minor grove (Manderville et al., 1994). Hydrolysis of its last amide bond leads to an inactive compound (bleomycinic acid). Replacement of this terminal sulfonium part by aminated moiety (bleomycin B2 or peplomycin) restore the activity.

Actinomicyn derivatives, which have been reviewed, are composed of a central aminophenoxazone and two cyclic peptidic side chains (for example: Val(NMe)Gly(NMe)-Pro-DVal) (Hollstein, 1974). These compounds were isolated from Streptomyces species. They bind to DNA *via* the intercalation of the central aminophenoxazone, and the side chains were shown to interact with the DNA minor groove. The relatively small alteration of the peptides made by the removal of the hydrophobic methyl of valine and glycine actually leads to a complete loss of cytotoxicity (Mosher and Goodman, 1972). It is noteworthy that peptide-anthraquinone derivatives have been prepared more recently and the specificity of their action studied (Ijaz et al., 2001; Takenaka et al., 1996).

### *V.2 Echinomycin and related compounds*

In the last 40 years a remarkable number of related antitumor DNA-interacting (Quigley et al., 1986; Takusagawa, 1985; Waring and Wakelin, 1974; Zhang and Patel, 1991) peptidic compounds were isolated and characterised. They display a general structure made of a central depsipeptide ring flanked by two quinoline or quinoxaline moieties. It is beyond the scope of this review to depict and compare all these structures. Echinomycin was the first to be isolated (Keller-Schierlein et al., 1959) and its proposed structure revised later (Dell et al., 1975). This was followed by triostin (Fig. 22) (Otsuka and Shõji, 1965; Otsuka et al., 1976), the closely related quinomycins (Martin et al., 1975; Williamson et al., 1982), BBM-928 / luzopeptin A (Fig. 22) (Arnold and Clardy, 1981; Konishi et al., 1981), quinaldopeptin (Toda et al., 1990), sandramycins (Matson and Bush, 1989; Matson et al., 1993), BE-22179 (Okada et al., 1994), quinoxyapeptins (Lingham et al., 1996), thiocoraline (Pérez Baz et al., 1997), korkormicins (Lam et al., 1995) and SW-163C and E (Takahashi et al., 2001). Echinomycin as been the subject of clinical trials, without notable results (Chang et al., 1998; Gradishar et al., 1995; Wadler et al., 1994).

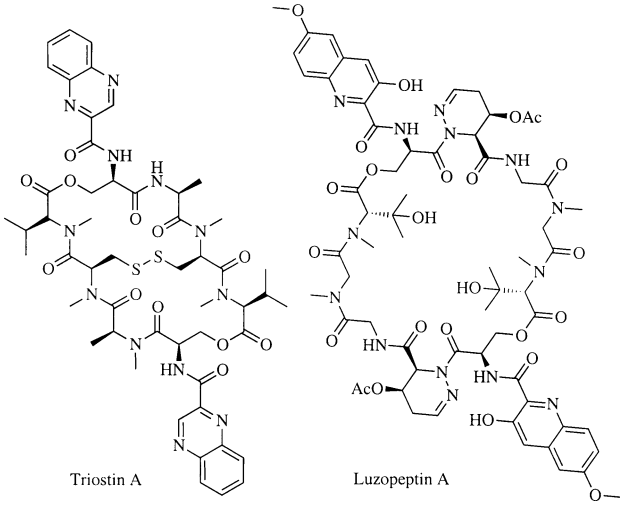



**Fig. 22.** Structures of triostin A and luzopeptin A

Structure-activity relationship studies were undertaken such as the synthesis of the bis-acridine analogue of des-N-tetramethyltriostin, which retained a high affinity for DNA (Helbecque et al., 1985). They were followed by much more extensive synthetic work on the luzopeptin-derived structures (Boger et al., 1998; Boger and Ichikawa, 2000; Boger et al., 1999; Boger and Saionz, 1999; Lam et al., 1995; Olsen et al., 1986). From them, some fascinating results were found for sandramycin analogues, such as an inhibition concentration for melanomas, carcinomas and adenocarcinomas in the picomolar range (Boger et al., 1998). On the mechanism of action point of view, quite remarkable specific effects were found. The depsipeptide BE-22179 was shown to preferentially inhibit topoisomerase II (Yoshinari et al., 1994), thiocoraline did not inhibit topoisomerases but DNA polymerase $\alpha$ (Erba et al., 1999) and quinoxapeptin did not inhibit any of the polymerase $\alpha, \beta, \gamma$ and $\delta$ but, as well as luzopeptin A, inhibited HIV-1 and HIV-2 reverse transcriptase (Lingham et al., 1996).

*V.3 Other examples*

Other examples of peptides that interact with DNA were found. Their structure is based on the sequences of transcriptionnal activators or other protein interacting with DNA. Remarkably simple peptides were studied such as the heptad repeat of polymerase II (Tyr-Ser-Pro-Thr-Ser-Pro-Ser-Tyr) (Khiat et al., 1996; Suzuki, 1990). For what it is worth, statistically-wise, the naturally occurring cytotoxic heptapeptide yunnanin C featuring the motif Tyr-Ser-Pro, was also reported (Morita et al., 1996b). Remarkably, the anti-cancer peptide X-Met-Leu-Pro-Ser-Tyr-Ser-Pro-Tyr, was identified from a soy proteins extract (Kim et al., 2000). Moreover, the tetrapeptides Ser-Pro-X-X, derived from netropsin, were also studied (Hao et al., 1995).

Other compounds are the 60-mer peptide bZIP motif (Tabor, 1996; Talanian et al., 1992), or the AT-DNA binding motif of mammalian high mobility group I (Thr-Pro-Lys-Arg-Pro-Arg-Gly-Arg-Pro-Lys-Lys) (Reeves and Nissen, 1990). Moreover, peptides comprising the RNA-binding motif Leu-Asp-X-Arg (X = an alkyl residue), involved in polyadenylation, were patented for blocking a specific kinase activity (Richter and Mendez, 2001).

## VI Other peptides

*VI.1 Linear peptides*

A remarkable number of endogenous pyroglutamate-starting growth regulatory peptides, such as pGlu-Glu-Asp-Ser-Gly and its analogues mentioned in the introduction were found (Balazs et al., 1992; Jensen et al., 1990; Laerum, 1990). The other peptides reported for a cellular growth inhibition are: pGlu-Phe-Gly-$NH_2$ (Gembistky et al., 2000), pGlu-Glu-Gly-Ser-Asp or pGlu-Glu-Gly-Ser-Asn (Paulsen et al., 1992), pGlu-Glu-Asp-Cys-Lys (Foa et al., 1987) or pGlu-His-Gly (Paulsen, 1993). The N-acetylated glutamate derivative Ac-Glu-Ser-Gly-$NH_2$ has also been found to inhibit lymphocyte growth (Liu et al., 2000c). Moreover the pineal-originated tetrapeptide Ala-Glu-Asp-Gly is reported to have a tumor suppressing effect (Khavinson and Anisimov, 2000). As a proper molecular mechanism of action of this class of peptide remain to be found, it is tempting to mention the dansylated octapeptide Dns-Glu-Asp-Asp-Ser-Asp-Glu-Glu-Asn reported for its antiproliferative action (Marsili et al., 1996). If this sequence is not exactly related to the above pGlu-starting compounds, it is remarkable that many phosphorylated peptides such as pGlu-Ala-Glu-Ser-Asn or pGlu-Asp-Asp-Ser-Asp-Glu-Asn can bind DNA in the presence of divalent cations (Cardellini et al., 1999; Chillemi et al., 1991). Among the puzzling facts concerning this last octapeptide is that a) the phosphorylated form is able to inhibit RNA polymerase II b) its sequence actually corresponds to the carboxy terminus section of the largest RNA polymerase II subunit c) this sequence actually follows the DNA-interacting heptad repeat of polymerase II mentioned in the previous section (Angiolillo et al., 1993).

- The bone marrow-extracted peptides Ac-Ser-Asp-Lys-Pro and Ser-Asp-Lys-Ac (Lenfant et al., 1989; Ruhenstroth-Bauer et al., 1993) or Phe-Arg-Pro-Arg-Ile-Met-Thr-Pro (Mikhailova et al., 1998; Strelkov et al., 2000) were reported for inhibition of cell proliferation. Structure-activity on the tetrapeptide Ac-Ser-Asp-Lys-Pro were undertaken in order to reduce its sensitivity toward proteases and to explore the respective importance of the peptide residues (Gaudron et al., 1999). They pointed out the importance of the central motif Ser-Asp-Lys (Thierry et al., 2001) which had actually been patented for its inhibition of the proliferation of liver cells (Ruhenstroth-Bauer, 1994; Ruhenstroth-Bauer, 1997).
- Tetrapeptides derived from phytotoxin AS-1, a severe toxin for plant leaves, such as Cys-Val-Gly-Glu; Tyr-Val-Gly-Glu and His-Val-Gly-Glu were cytotoxic to mouse fibroblast L929 (Liakopoulou-Kyriakides et al., 1998).
- Many other simple linear peptides listed here have been isolated or prepared and reported for an anticancer potential: copper complex of Gly-His-Lys (Pickart, 1989); Palmitoyl-Leu-Leu-Arg-OMe (Ueda et al., 1986); enkephalin aldehydes H-Tyr-Gly-Gly-Phe-Met (or Val)H and enkephalin analogues (Daiichi and Yakuhin, 1985; Scholar et al., 1987); segments of Asn-Gln-Asn-Gly-Ser-Asn-Pro-Lys-The-Val-Lys-Gln-Ala, isolated from *Papaver somniferum* pollen (Xu and Jin, 1998); Leu-Ile-Glu-Asp-Asn-Glu-Tyr-Thr-Ala-Arg (Sagami, 1984) or the 16-mer sequence, pGlu-Leu-Lys-Cys-Tyr-Thr-Cys-Lys-Glu-Pro-Met-Thr-Ser-Ala-Ala-Cys, obtained from the amino terminal fragment of a urine-extracted antineoplastic protein (Ridge and Sloane, 1996; Sloane, 2002).

– More elaborate linear cytotoxic peptides were also characterised such as the two linear peptides, majusculamide D and deoxymajusculamide D (Fig. 23) (Moore and Entzeroth, 1988). The closely related microcolins were reported for their immunosuppressive properties, and their apoptosis induction (Koehn et al., 1992; Zhang and Longley, 1999). It is noteworthy that a mixture of, at least, 16 very lipophilic peptides named roseoferin was shown to have high antiproliferative effect (Degenkolb et al., 2000). The cytotoxic and quite lipophilic 18-mer AcPhe-Aib-Ala-Aib-Iva-Leu-Gln-Gly-Aib-Aib-Ala-Ala-Aib-Pro-Iva-Aib-Gln-Trpo was isolated from *ascomycetes Apiocra sp*. (Kim et al., 2002). Moreover adenopeptin, a fairly simple lipid-containing tridecapeptide was shown to induce apoptosis in transformed cells (Hayakawa et al., 1998).

### *VI.2 Cyclic peptides*

The cyclodepsipeptide dolastatin 14 (Fig. 24), containing a 14 carbon long lipophilic hydroxy acid, was isolated from sea hare *Dolabella auricularia* and was found to be very active (Pettit et al., 1990). The lack of available sample is probably the reason for the absence of experimental data on its mechanism of action. The remotely related aurilide bearing another lipophilic hydroxy acid was isolated from *Dolabella auricularia* and a synthetic sample is still very cytotoxic (Mutou et al., 1997). Dolastatin G (Mutou et al., 1996a; Mutou et al., 1996b) and lyngbyastatin 2 are compounds actually sharing some common components with these peptides. However, lyngbyastatin 2 was only found toxic on mice (Luesch et al., 1999).

Papuamides (Fig. 25) are depsipeptides displaying a lipophilic decanedienoic side chain that have been isolated from the sponges *Theonella mirabilis* and *Thoenella swonhoei* and display powerful anti HIV and cytotoxic properties (Ford et al., 1999). Although it is 6-hydroxylated, an homoproline residue is also present in a number of much less cytotoxic depsipeptides such as microcystilide (Tsukamoto et al., 1993), dolastatin 13 (Pettit et al., 1989b), symplostatin 2 (Harrigan et al., 1999) or somamides (Nogle et al., 2001).

The strongly cytotoxic tetradecapeptide discodermin E (Fig. 26) was isolated from the marine sponge *Discodermia kiiensis* (Ryu et al., 1994a). Many related compounds have been reported such as: discodermins A-D, F-H (Matsunaga et al., 1984; Matsunaga et al., 1985a; Matsunaga et al., 1985b; Ryu et al., 1994b), polydiscamide A (Gulavita et al., 1992) and halicylindramide (Li et al., 1995a; Li et al., 1996).

Kalahalide F (Fig. 27), is a potent antitumor cyclic depsipeptide isolated from the sarcoglossan mollusc *Elysia rufescens* and its diet, the green alga *Bryopsis sp* (Goetz et al., 1999; Hamann and Scheuer, 1993). A recent patent describes the structure-activity studies that led to a lithocholoyl-containing analogue (Fig. 27) which is more potent than kahalalide F (Albericio et al., 2002; López-Macià et al., 2001). Their remark-

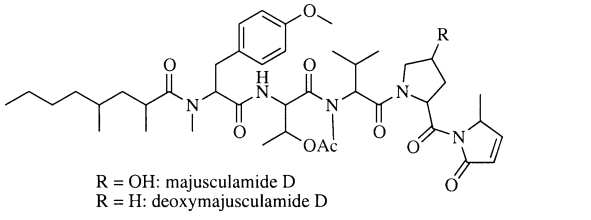



**Fig. 23.** Majusculamide D and deoxymajusculamide D

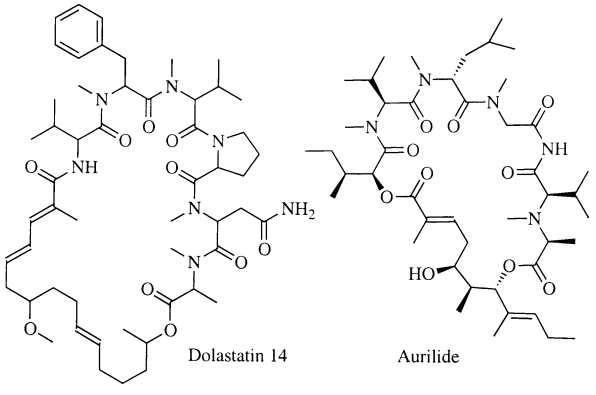



**Fig. 24.** Dolastatin 14 and aurilide

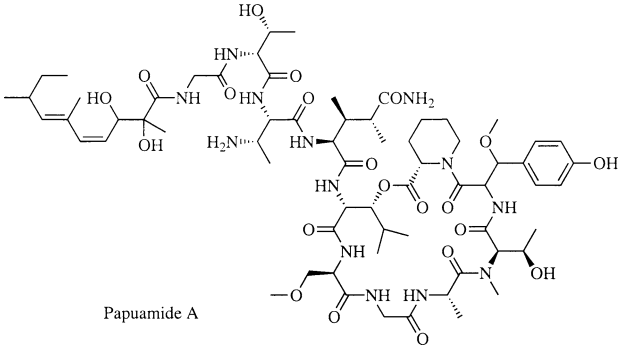



**Fig. 25.** Papuamide A

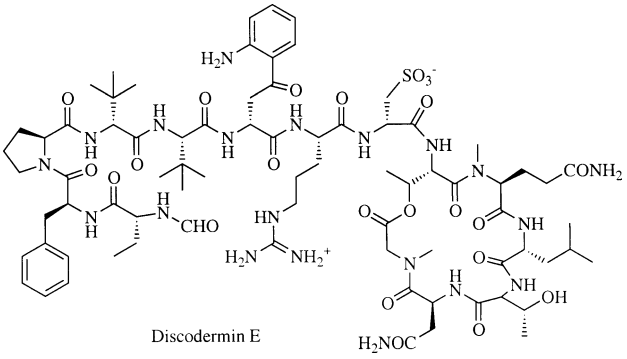



**Fig. 26.** Structure of discodermin E

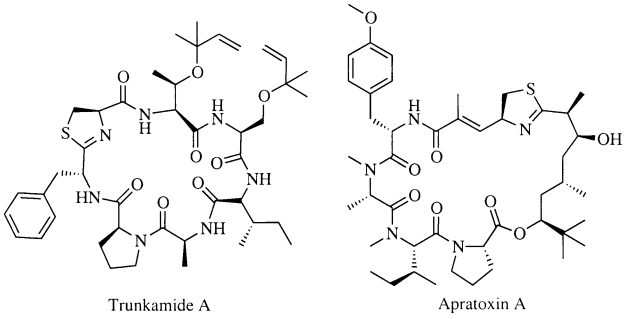



**Fig. 28.** Trunkamide A and apratoxin A

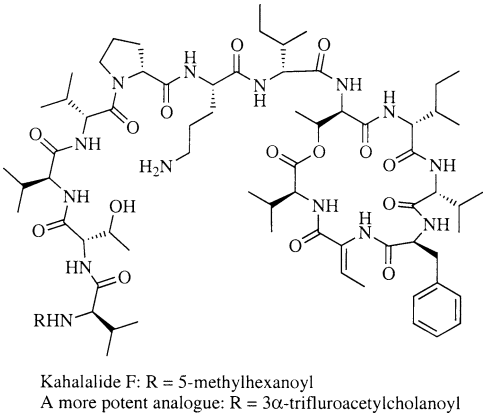



**Fig. 27.** Kahalalide F and its more potent analogue

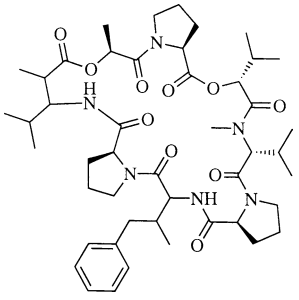


**Fig. 29.** Dolastatin 16

able structural similarities with compounds such as discodermin E (Fig. 26) hold the promises of future synthetic studies. A dehydrobutyric residue has also been found in the structures of cytotoxic dolastatin 13 and other related compounds (Pettit et al., 1989b).

Many cytotoxic thiazole-containing cyclopeptidic compounds have been isolated. We will just depict trunkamide A (Caba et al., 2001; Carroll et al., 1996a; Wipf and Uto, 1999) and apratoxin A (Luesch et al., 2002; Luesch et al., 2001c) (Fig. 28) which are notable in terms of cytotoxicity. However, apratoxin A was found only marginally active *in vivo*. Other reported cytotoxic peptides containing thiazoles and/or oxazoles are: ulithiacyclamide (Ireland et al., 1982; Shioiri et al., 1987; Williams et al., 1989), dolastatin 3 (Pettit et al., 1987), ulicyclamide (Kohda et al., 1989), keramamide F (Itagaki et al., 1992), mollamide (Carroll et al., 1994), patellamide 6 (Carroll et al., 1996a), keenamide A (Wesson and Hamann, 1996), lissoclinamide 7 (Hawkins et al., 1990), orbiculamaide A (Fusetani et al., 1991), westiellamide (Wipf and Miller, 1992), cyclodidemnamide (Toske and Fenical, 1995), oriamide (Chill et al., 1997), keramamide K (Uemoto et al., 1998), keramamide M and N (Tsuda et al., 1999), microcyclamide (Ishida et al., 2000) and waiakeamide (Mau et al., 1996) or the related haligramides (Rashid et al., 2000).

Dolastatin 16 (Fig. 29) also isolated from *Dolabella auricularia*, but from another part of the sea world, was found very cytotoxic (Pettit et al., 1997a). Other depsipeptides, featuring a $\beta$-amino acid, were reported such as cyclic octapeptides made of Asn-Tyr-Asn-Gln-Pro-Asn-Ser and various fatty $\beta$-amino acids (Ikegami et al., 1987), dolastatin D (Sone et al., 1993a) and dolastatin 17 (Pettit et al., 1998b). A remarkable series of cyclo-$\beta$-tripeptides, bearing lipophilic sides chains, have been recently reported (Gademann and Seebach, 2001). Moreover the cytotoxic kailiuns (Harrigan et al., 1997) and pitipeptolides (Luesch et al., 2001b) display a fatty side chain as well as lipophilic residues. Also reported for their cytotoxicity are the lipophilic cyclic peptides axinellins (Randazzo et al., 1998), cycloleonuripeptides (Morita et al., 1996a), mollamide (Carroll et al., 1994) and onchidins (Fernández et al., 1996).

Many other cytotoxic peptides of natural origin could be depicted here either for their remarkable structure or their antitumor potential. As a chemist we would mention peptides bearing a challenging structure such as the kapakahines (Yeung et al., 1996), the himastatin (Kamenecka and Danishefsky, 1998; Mamber et al., 1994) and the related chloptosin (Umezawa et al., 2000), the theonellamides (Matsunaga and Fusetani, 1995), the aciculitins (Bewley et al., 1996), the microsclerodermins (Qureshi et al., 2000) and the cyclocinamide (Clark et al., 1997; Grieco and Reilly, 1998). Indeed all these cytotoxic peptides bear remarkable structures arising from further chemical reaction on the amino acid residues. Total synthesis of these compounds and their analogues, coupled with proper biological studies of their mechanism of action, could lead to original approaches to antitumor therapy.

## VII Conclusions

This review is incomplete in at least two different ways. First, for all the relevant papers that were overlooked we have to apologise. The isolation, characterisation, design, synthesis/biosynthesis and biological testing of these compounds have been a tremendous task, undertook and achieved by many. Second, quite often, either when a common mechanism of action was known or not, some tantalising structural similarities between "unrelated" compounds were noticed. In this regard the present review is seriously faulty since only peptides were reviewed. Only one case of linear similarity such as the one described in the introduction was found in the course of this work (see the end of the nucleic acid-interacting agents section). However, a future achievement will be to be able to pinpoint three dimensional structural similarities for any type of compound and thus maybe, by analogy, suggest a common biochemical mechanism of action.

The remarkable phage-displaying method or the peptide aptamer screening and other related techniques have provided many peptides of potential interest. The most though provoking could be work describing tripeptides (derivatives of Pro-Thr-Trp, Pro-Tyr-Pro-$NH_2$ or Glu-Arg-Pro), found *via* a screening, which suppress cell proliferation (Hiwasa et al., 1996; Ike et al., 1997). One may forecast for the near future a landslide of new peptidic structures, targeting many original cellular mechanisms, which will have to be chemically "adapted" to the stringent requirement of cellular and mammalian pharmacology to yield marketable drugs. This is not a small task as its complexity is "exponentially more laborious with the starting peptide length" (Huber et al., 1994). On the other hand, nature also provides an access to a quite infinite number of secondary metabolites and, as analytical techniques have been improving enormously, it is a noteworthy source of original and already organism-adapted peptidic structures. As a final point to this review, the remarkable cyclic peptide Ser-Arg-His-Lys-Lys-D-Ala (Fig. 30) has been recently patented (Halazonetis and Hartwig, 2001) for its p53 activation properties. The "simplicity" of its structure is in itself an humbling lesson.

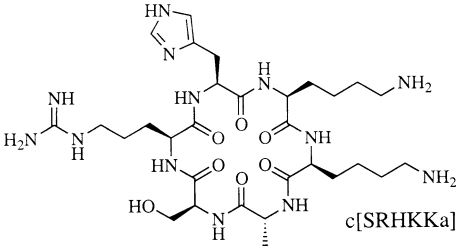



**Fig. 30.** A man-made activator of p53

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**Note added in proof**

Concerning cell signalling, a remarkable book entitled "Signal Transduction" written by Gomperts BD, Kramer IM and Tatham PER (Academic Press) is a very good comprehensive contribution illustrating the complexity of the all the proteins involved.

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