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1 Naturally-occurring Antitumour Agents

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INTRODUCTION

Plants have been used in the treatment of malignant diseases for thousands of years [1–3], but the studies of Dustin in 1938 on the cytotoxicity of colchicine heralded the start of the search for natural antimitotic drugs [4]. During the last 25 years, research into this branch of natural products proliferated with the result that a large number of experimentally-interesting antitumour agents have been found, yet only a few of which are used clinically. The purpose of this review is to give a brief account of the methods used for detecting antitumour activity and selecting drugs for clinical trial, and then to outline the chemistry and pharmacology of compounds derived from plants which possess antitumour activity. Active compounds isolated from the higher plants and ferns will be discussed and, where appropriate, substances obtained from fungi and bacteria will be considered. Compounds are classified according to the functionality responsible for the activity rather than according to the classes of natural products, such as alkaloids and steroids.

METHODS USED FOR DETECTING ANTITUMOUR ACTIVITY

A number of methods have been developed for detecting antitumour activity, all of which are a compromise between the desirable and the practicable. The main test system employed is the transplanted animal tumour. Other tests, such as spontaneous and induced tumour systems, tissue culture techniques, and anti-microbial and biochemical tests, are used to a lesser extent [5].

TRANSPLANTABLE TUMOURS

A large number of transplantable tumour systems have been developed for detecting antitumour activity [5, 6]. These tests measure the effect of compounds on rapidly developing primary tumours produced by transplantation of experimental tumours in animals. More recently, attempts have been made to develop test systems capable of measuring the effect of compounds on metastases produced by the primary tumours [7].

Several factors should be considered in the design of a suitable test procedure; (1) to evaluate the significance of the results obtained, and (2) to determine whether or not the compound under test should be selected for pre-clinical toxicological studies and subsequent clinical trials. These include the choice of animal and tumour to be used in the trial, and the method of administering the compound, measuring the effect of the compound on tumour growth, and evaluating the effect of the drug on healthy tissues.

(*a*) *Animals*—Random-bred animals are generally adequate for primary tests, but inbred animals or their F1 hybrids are essential for dose-response studies, for comparisons of two or more drugs, and for the determination of therapeutic ratios. Animals of the same sex should be used for any one test. When a transplantable tumour is chosen, by definition the animal is also selected, but with those tumours which grow on several strains it is necessary to select the best strain for the particular experiment. The species mainly used for transplantable tumour experiments are rats and mice.

(*b*) *Tumours*—Almost any malignant tumour, spontaneous or induced, is potentially transplantable within a limited number of species. However, the usefulness of a tumour can only be assessed after it has achieved a certain degree of genetic and antigenic stability and hence its reliability is predictable.

Tumours used for antitumour tests should be stable, undifferentiated and antigenically neutral; they can be obtained by serial transplantation of the tumour from animal to animal. During the early stages of serial transplantation, tumours retain a recognisable similarity with the original and may only grow in a limited number of hosts into which they are grafted. At a later stage regression occurs, with subsequent loss of the tumour's recognisable features and an increased take-rate in homologous hosts of entirely different genetic composition [8].

Many attempts have been made to develop transplantable tumours as models for the study of specific human cancers. Thus, the Cloudman S91 melanoma was developed to select drugs for use in the treatment of human melanoma [9], and plasma cell tumours as models for multiple myeloma [10]. The greatest disadvantage of this approach is that tumours tend to lose their special characteristics very rapidly during serial transplantation, with the result that the tumour obtained is similar to those originating from different tissues. An extension of this approach would be the matching of human cancers with transplantable tumours having similar enzyme content and other biochemical features.

Tumours are usually obtained frozen or *in situ* in the animals into which they have been transplanted. No tumour should be used for the detection of antitumour activity until it has passed through at least three generations of animal, and it is advisable to carry out stringent bacteriological examinations on the new tumour before use [11].

The objective of transplantation is the introduction of an adequate amount of viable tumour tissue at a chosen site under aseptic conditions [12]. Hair is removed from all parts of the body of the donor and at the point of injection of the recipient, and the areas sterilised with disinfectant before transplantation is effected. Solid tumours are introduced subcutaneously or intramuscularly as tumour minces, cell suspensions or solid pieces, whilst ascitic tumours are introduced by intraperitoneal injection. From a large tumour it is usually possible to graft 30–100 animals, depending on the method of grafting and the type of tumour.

(*c*) *Method of administering test compounds*—The compound is administered as a solution in water, saline, dimethylformamide, aqueous dimethyl sulphoxide, fixed oils, or propylene glycol, or as a suspension in carboxymethylcellulose, methylcellulose or steroid suspending solution [1]. It is introduced by the intraperitoneal, intravenous or oral routes, or by subcutaneous injection into the opposite flank. The number of injections and the time intervals between them vary from a single dose to multiple doses given at daily or longer intervals; the method employed is dependent on the compound under study. It is customary to commence injections on the day after tumour transplantation, as this ensures that the test substance reaches the centre of an established tumour, a condition not always satisfied in large neoplasms [13], although it does mean that in some cases remission may be associated with interference with the implantation mechanism rather than with antitumour activity.

(*d*) *Measuring the effect of the compound on tumour growth*—Each experiment should consist of at least three groups: a test group, a positive control group treated with a known antitumour agent, and a solvent-only control group. The number of animals used per group should be the fewest compatible with detecting activity [14]. Animals are weighed at the beginning, during and on completion of the test to check for toxicity of the com-

pound under test. In tests using transplantable leukaemias, regular blood counts are taken, and with solid tumours, the size of the tumour growth is measured regularly with calipers. Assessment of the effect of the test substance on tumour growth can be made by measuring at a fixed interval of time after transplantation the change in tumour size or weight of solid tumours, or the survival time, total packed cell volume or white blood cells for ascites tumours or leukaemias. Results are expressed as the mean percentage inhibition of tumour growth or as simple ratios of test/control (T/C). For solid tumours, significant activity is achieved when tumour weight inhibition is greater than 58 per cent (T/C 0·42), whereas for leukaemias and ascites tumours this is achieved with an increased life span of 25 per cent or more (T/C $\geqslant$ 1·25) [14].

(*e*) *Selection of compounds for clinical trial*—Selection of compounds for clinical trial is made on the basis of the test substance passing a selected screen of transplanted tumours and showing no deleterious side-effects in pre-clinical pharmacological and toxicological studies [15]. The number and type of tumours used in the screen varies from worker to worker: selection of a drug for clinical study may be made on the basis of a very high activity against a single tumour or because the compound shows significant activity against a wide spectrum of neoplasms. The Cancer Chemotherapy National Service Centre (CCNSC), which has tested thousands of synthetic and naturally-occurring compounds for antitumour activity, have used in the past a large number of mouse, rat, and hamster tumours in the primary screen [16], such as adenocarcinoma 755, Cloudman melanoma S91, Lewis Lung carcinoma, Sarcoma 180, Lymphoid leukaemia L 1210, and Walker 256 (intramuscular and subcutaneous forms). In more recent studies, this Centre has reduced the screen to two tumours, L 1210 and Walker 256 (intramuscular), and latest reports show that the latter neoplasm has now been eliminated from the screen [7]. Another factor used in selecting a compound for clinical trial is its therapeutic index. This is the ratio of the minimum tolerated dose (the LD_{10} value, determined in animals bearing the tumour) to the minimum effective dose. A compound is not usually selected for clinical study unless it has a therapeutic index greater than 2 [1].

SPONTANEOUS TUMOURS

Spontaneously occurring animal tumours were initially the system of choice for testing compounds for antitumour activity because of their close resemblance to human carcinomas. Use of these systems is restricted by three factors; the unpredictable time of appearance and low incidence of tumours, the choice of tumours available for testing, and the difficulties in diagnosing and measuring regressions in tumours other than those appearing in easily accessible sites.

INDUCED TUMOURS

Tumours may be induced at various sites in a variety of animals by physical, chemical and viral agents. Chemical induction is the method most frequently used and involves tumour induction by carcinogenic compounds. Thus, 3,4,9,10-dibenzopyrene induces fibrosarcomas in weanling Swiss mice within 10–15 weeks of subcutaneous implantation [17]. Two virally-induced tumours have been used for detecting antitumour activity. These are the Friend leukaemia [18] and Rous sarcoma [19]. The former system is of interest as it is sensitive to a wide spectrum of antitumour agents.

The main disadvantages of induced tumours for detecting antitumour activity are the difficulties involved in obtaining sufficient numbers of animals for testing at the same time, and the removal of the implanted carcinogen after tumour induction.

HETEROPLANTED HUMAN TUMOURS

Efforts have been made to find suitable sites to grow transplanted human tumours, and these have resulted in the development of three systems capable of detecting antitumour activity. First, the hamster cheek pouch is a suitable site for heterotumour transplantation as it is protected from the immunological defence mechanism of the hamster [20]. The hamsters are often pretreated with cortisone prior to transplantation to reduce the animal's immunological defence mechanism and aid transplantation. Second, a combination of cortisone and x-rays is also used to reduce an animal's immunological defence mechanism and thus make it a suitable vehicle for transplanted human tumours [21]. However, the optimal method for conditioning animals varies with species. Thus, the rabbit and hamster require cortisone alone, whereas the rat requires a combination of cortisone and x-rays to produce the greatest success. Third, embryonated eggs may also be used for the growth of heterologous tumours [22]. Studies with 19 clinically active drugs have shown that this system is capable of detecting antitumour activity for each compound [23]. The major criticism of this method is that the serially transplanted human tumours bear little relationship to the cancers from which they originated.

TISSUE CULTURE TECHNIQUES

Systems have been developed which enable human tumours to grow in tissue culture. The cells may be cultured in various ways and, depending on the method employed, different measurements of activity of drugs on the tumour cells are used. Direct counting of viable cells is employed when

the cells are grown in a monolayer on a cover slip [24], whereas the method of Miyurama [25], in which the cells are grown on agar plates and exposed to the drug contained in porcelain cylinders, involves the use of methylene blue. Inhibition of growth results in the plate remaining blue, whereas decolorisation shows the presence of growing cells. Other methods involve the determination of light transmission through the medium in which the cells are growing [26], and the use of cytological data such as increased cellular debris, nuclear changes, and cytolysis for the detection of antineoplastic activity [27]. The KB cell line, in which human epidermoid carcinoma of the nasopharynx is cultured on Eagle's basal medium, has been used extensively by the CCNSC as a primary screen for detecting cytotoxicity in plant extracts [14]. They have found good correlation between *in vitro* cytotoxicity and antitumour activity against transplantable tumour systems. Tissue culture techniques have also been used for testing drugs against human tumour samples removed during an operation or biopsy to determine the effectiveness of the drug against the tumour [28].

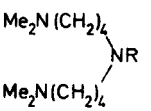
ANTIMICROBIAL TESTS

Antimicrobial test systems have been used to a limited extent for the detection of antitumour activity. It is assumed that a compound which inhibits bacterial cell growth and multiplication has a similar activity on cancer cells, as the two share similar metabolic pathways. The technique, however, has had limited success with anti-metabolites [29]. It is unlikely that this test system will ever replace a tumour system for the determination of carcinostatic activity [30].

TERTIARY AMINES

ACYCLIC TERTIARY AMINES

Two acyclic alkaloids, solapalmitine (Ia) and solapalmitenine (Ib), isolated from the Bolivian plant *Solanum tripartitum*, have been shown to have *in*



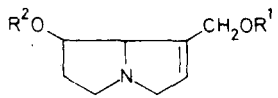
(I)

(a) $R = CO(CH_2)_{14}Me$
(b) $R = trans\text{-}CO{\cdot}CH{=}CH(CH_2)_{12}Me$

vivo activity against Walker 256 [31, 32]. Their therapeutic indices do not warrant further pharmacological studies on the molecules, but structure-activity relationship investigations on analogues seem justified [33].

PYRROLIZIDINES

Pyrrolizidine alkaloids, a large group of plant bases, have been known for some considerable time to possess pharmacological activity, and in particular hepatotoxicity [34]. Recent studies have revealed that certain members of this class of alkaloids display antitumour activity against Walker 256, Ca 755, and S 180, and do not have significant cytotoxicity [35]. Structure-activity relationship studies have shown (a) that the active alkaloids include retronecine (IIa), mono- and di-esters of monobasic acids, cyclic esters of dibasic acids, and some *N*-oxides of these alkaloids, and (b) that four cyclic diesters of retronecine and unesterified amino alcohols are inactive. From



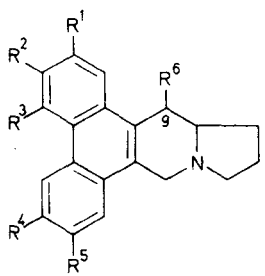
(II)

(a) $R^1 = R^2 = H$
(b) $R^1, R^2 = CO{\cdot}CMe(OH){\cdot}CMe(OH){\cdot}CHMe{\cdot}CO$
(c) $R^1, R^2 = CO{\cdot}CMe(OH){\cdot}CMe(OAc){\cdot}CHMe{\cdot}CO$

these studies, no effective structure-activity relationships in this group of alkaloids can be made. Monocrotaline (IIb) and spectabiline (IIc) have therapeutic indices of greater than 17 and 7 respectively against Walker 256 and would be considered suitable for clinical studies were it not for their reported hepatoxicity [36].

PHENANTHROINDOLIZIDINES

Systematic fractionation of an extract of *Tylophora crebriflora* has furnished six new alkaloids related to tylophorine (IIIa) which possess antitumour activity [37]. These alkaloids and several known phenanthroindolizidines have been tested against a number of experimental neoplasms [38]. Tylocrebrine (IIIb) is active against Ca 755, Murphy Sturm Lymphosarcoma, P-388 lymphocytic leukaemia and L 1210; tylophorine (IIIa) against



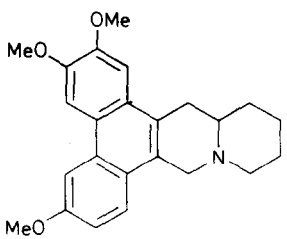
(III)

(a) $R^1 = R^2 = R^4 = R^5 = OMe$; $R^3 = R^6 = H$
(b) $R^1 = R^6 = H$; $R^2 = R^3 = R^4 = R^5 = OMe$
(c) $R^1 = R^6 = H$; $R^2 = R^4 = R^5 = OMe$; $R^3 = OH$
(d) $R^1 = H$; $R^2 = R^4 = R^5 = OMe$; $R^3 = R^6 = OH$
(e) $R^1 = R^2 = R^3 = R^4 = R^5 = OMe$; $R^6 = OH$
(f) $R^1 = R^2 = R^3 = R^4 = R^5 = OMe$; $R^6 = H$
(g) $R^1 = R^3 = H$; $R^2 = R^4 = R^5 = OMe$; $R^6 = OH$
(h) $R^1 = R^2 = R^3 = R^4 = R^5 = R^6 = H$

L 1210; (IIIc) against Ca 755 and W 256; (IIId) against S 180, Ca 755, W 256, L 1210 and P 1534 leukaemia; (IIIe) against L 1210; (IIIf) against W 256; and tylophorinine (IIIg) against L 1210 respectively. It is interesting to note that phenanthroindolizidine (IIIh) is inactive, that slight changes in the substitution pattern on the phenanthrene moiety does not destroy activity, that substitution of OH at C-9 increases the activity, and that compounds possessing both phenolic and benzylic hydroxyls are the most active [39]. Tylocrebrine (IIIb) was selected for pharmacological investigation and clinical study, but unexpected irreversible CNS toxicity observed in the clinic has necessitated the termination of these trials pending further study. The chemistry of the *Tylophora* alkaloids has been reviewed recently [40a], and a new synthetic method has been described [40b].

PHENANTHROQUINOLIZIDINES

Recent studies on extracts of *Boehmeria cylindrica* have shown that cryptopleurine (IV) has a highly specific and extremely cytotoxic action against

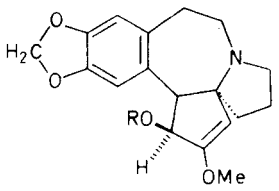


(IV)

Eagle's 9 KB carcinoma in cell culture ($ED_{50} = 7{\cdot}8 \times 10^{-4}$ μg/ml), but is inactive *in vivo* against a number of experimental neoplasms [41]. A biogenetically-based synthesis of cryptopleurine has recently been described [42]. A number of analogues of (IV) have been synthesized for antitumour studies [42a].

HARRINGTONINE AND ISOHARRINGTONINE

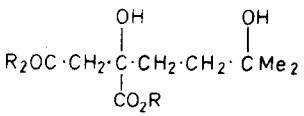
Several new alkaloids have been isolated recently from *Cephalotaxus harringtonia* var. *drupacea*, two of which, harringtonine (Va) and isoharringtonine (Vb), show inhibitory activity against L 1210 and P388 at dose levels of 0·25 to 4 mg/kg and 0·75 to 12 mg/kg respectively [43, 44]. The structure of the heterocyclic portion of these molecules has been established [45] by spectroscopic and x-ray crystallographic studies on cephalotaxine and its methiodide, and the terpenoid portion by spectroscopic analysis of



(V)

(a) R = monomethyl ester of (VIa)
(b) R = isomeric monomethyl ester of (VIa)

the ester (VIb). The point of attachment of cephalotaxine to the monomethyl esters of the dicarboxylic acid (VIa) in the molecules has yet to be defined. It is interesting to note that in this group of compounds antitumour activity is only observed in those alkaloids which contain the terpenoid moiety.



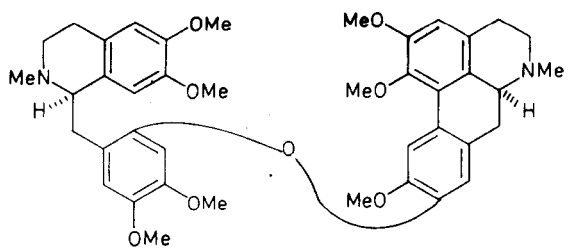
(VI)

(a) R = H
(b) R = Me

DIMERIC TETRAHYDROISOQUINOLINES

Thalicarpine

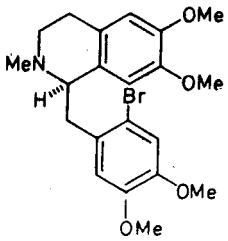
Systematic fractionation of extracts of *Thalictrum dasycarpum* root resulted in the isolation of thalicarpine (VII), one of a new group of dimeric isoquinoline alkaloids which have antitumour activity [46]. The alkaloid has subsequently been isolated from *Thalictrum minus* spp. *elatum* [47], *T.*



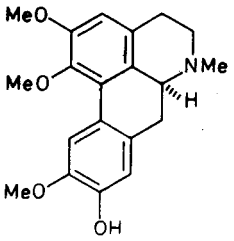
(VII)

revolutum [48] and *Hernandia ovigera* [49], and the chemistry of thalicarpine has recently been reviewed [50]. Synthesis of thalicarpine has been accomplished by Ullmann condensation of (S)-(+)-6-bromolaudanosine (VIII)

with (S)-*N*-methylaurotetanine (IX); this established the absolute configuration of the molecule [51]. Its total synthesis has been reported [51a]. A preclinical toxicological study of the thalicarpine has shown that the drug has single dose i.p. and oral LD_{50} values for mice of 247·2 and 1543·5 mg/kg,



(VIII)

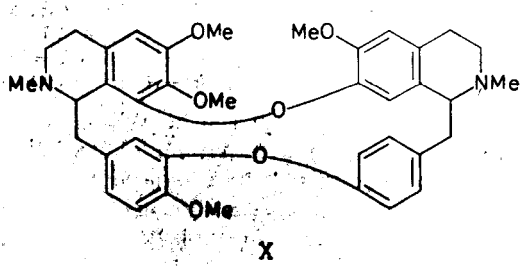


(IX)

and an i.v. value for rats of 500 mg/kg. When 15·6 mg/kg was administered to a dog, polypnea, slight to moderate bilateral râles, and mydriasis were produced, and increases in the heart and respiratory rates were observed on days 2 to 4. With higher doses, mydriasis and dose-related cardiopulmonary effects were produced, and death resulted from cardiac arrest. Post-mortem examination of dogs which succumbed to the drug showed pulmonary oedema, emphysema and haemorrhage, congestion of lung, kidney and liver tissues, and myocardial ventricular oedema and swelling. No evidence was found to suggest a continued build-up of the compound in tissues, and this may account for the absence of delayed toxicity in dogs receiving repeated intravenous doses [52].

Tetrandrine

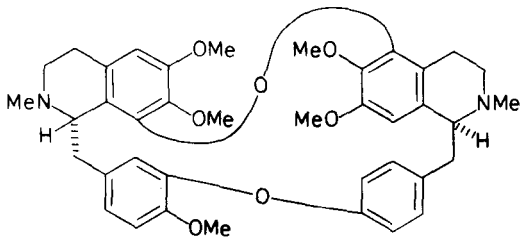
Investigation of the cytoxic agents of *Stephania hernandifolia* showed that both enantiomorphs and the racemic modification of tetrandrine (X) have significant *in vivo* activity against W 256. With a therapeutic index of greater than 2, (±)-tetrandrine warrants preclinical pharmacological study [53, 54]. A new synthetic route to the tetrandrine skeleton has been recently reported [55].



X

Thalidasine

A new bisbenzylisoquinoline alkaloid, thalidasine (Xa) has been isolated from *Thalictrum dasycarpum* [56] and *T. rugosum* [57] and shown to be active against W 256. The therapeutic index of thalidasine is greater than 1·5

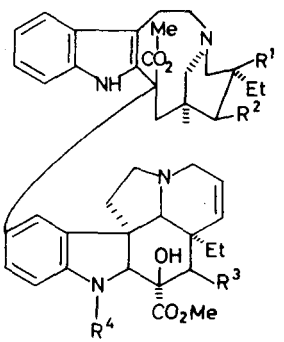


(Xa)

against this experimental tumour [54]. The antitumour activity of a number of dimeric isoquinolines have been studied, but no conclusions can be drawn from this evidence regarding the structural features necessary for activity [54].

DIMERIC INDOLE ALKALOIDS

The genus *Catharanthus* (fam. Apocynaceae) is a prodigious producer of alkaloids. To date, some 72 alkaloids have been isolated from plants of this genus, of which 24 are dimeric indoles. Six of the dimeric indole alkaloids, vinblastine, vincristine, vinleurosine, vinrosidine, leurosidine, and rovidine



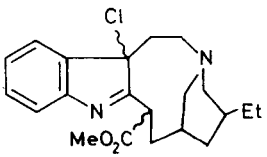
(XI)

(a) R^1=OH; R^2=H; R^3=OAc; R^4=Me
(b) R^1=OH; R^2=H; R^3=OAc; R^4=CHO
(c) R^1=H; R^2=OH; R^3=OAc; R^4=Me
(d) R^1,R^2=O; R^3=OAc; R^4=Me
(e) R^1=R^2=H; R^3=OAc; R^4=Me
(f) R^1=OH; R^2=H; R^3=OCO·CH_2·NMe_2; R^4=Me

have anti-neoplastic activity [58]. Vinblastine (XIa) and vincristine (XIb) are the most important alkaloids of this group as they have both been used successfully in the treatment of human neoplasms.

The chemistry of vinblastine and vincristine has been reviewed [59, 60]. The constitutions of vinrosidine (XIc) and vinleurosine (XId) have recently been reported [61]; these followed from chemical and spectroscopic studies on the alkaloids. A new synthetic sequence leading to dimeric indole alkaloids has recently been described [62], and this may find application in the synthesis of the natural dimers. Condensation of the chloroindolenine (XII) and vindoline (XIII) gave the dimer (XIe).

Chemical modification of vinblastine has shown that antileukaemic activity against P-1534 is destroyed by removal of the acetoxy group, acetylation of the tertiary hydroxyls, or reduction of the methoxycarbonyl groups



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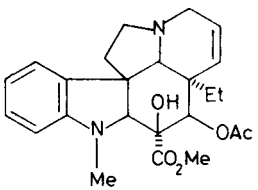

(XIII)

to the corresponding carbinols. Other chemical changes do not affect activity. Thus, oxidation of R^4 from methyl to formyl (XIa,b), variation of the substituents R^1 and R^2 (XIb,c,d), quaternisation of the basic nitrogen of the indole moiety with various alkyl halides, or replacement of the acetoxyl group (R^3) with $O{\cdot}CO{\cdot}CH_2X$, where X = CL, CN, or NR′R″ and R′R″ are alkyl groups or part of a heterocyclic ring, do not destroy activity [59].

Biochemical studies on the oncolytic dimeric indole alkaloids have shown that vinblastine and vincristine are mitotic spindle poisons and inhibit RNA synthesis [63, 64]. Vinleurosine has been found to inhibit the uptake of uridine-^{3}H and the incorporation of this nucleoside into RNA, of glutamic acid-^{14}C into proteins, and of acetate-^{14}C into lipids, during *in vitro* and *in vivo* studies with S 180. Incorporation of acetate into phospholipids was most sensitive to the inhibitory effect of the alkaloid [65].

Vinblastine

The sulphate of this alkaloid has been used mainly for the treatment of Hodgkin's disease, reticulum cell sarcomas, lymphosarcomas, monocytic leukaemias, choriocarcinomas, and mammary and ovary carcinomas [66–70a]. It has been used also in combination with vincristine for the treatment of acute lymphocytic and myeloblastic leukaemias in children [71]. Toxic

effects observed in the clinic are leukopenia, minor neurological symptoms, such as sporadic pains of the stiffness type, which are often associated with fever; depression of the tendon reflexes, maxillary pains followed by abdominal pains, and occasional anaemia and thrombocytopenia [66]. Vinblastine has also been observed to cause erythrema and occasional vesiculation and desquamation in patient's skin previously irradiated with x-rays [72]. Use of the drug for treatment of gestational trophoblastic neoplasms does not appear to affect mammalian oocytes or produce possible hazards to mother or foetus in subsequent pregnancies [73].

Vincristine

Vincristine sulphate has been used alone and in combination with prednisone for the treatment of acute lymphoblastic leukaemia: remissions have been induced also in lymphosarcomas and Hodgkin's disease [66, 74–79]. It has been claimed to be suitable for the management of other tumours [70a, 80, 80a]. No effective remissions have been observed, however, in patients with brain tumours [81]. The duration of cytotoxic activity of vincristine in the blood of leukaemic children is two to four hours [82].

Vinglycinate

Structure-activity studies have led to the development of vinglycinate sulphate (XIf). Administration of the drug to 31 patients with malignant diseases has resulted in beneficial response with Hodgkin's disease, lymphosarcoma, bronchogenic carcinoma, and chondrosarcoma. There is a lack of cross-resistance between vinglycinate and vinblastine or vincristine, and the dose required is approximately ten times that of vinblastine. Leukopenia is the dose limiting factor [83].

Vinleurosine

Vinleurosine has been disappointing in clinical trials [84, 85]. It has been suggested that its lack of activity might be due to binding by plasma proteins or some other form of inactivation [65].

HETEROCYCLIC AMINES

PYRIMIDINES

The pyrrolo[2,3-d]pyrimidine nucleoside antibiotic sangivamycin (XIVa), isolated from an unidentified species of *Streptomyces*, has *in vitro* activity