Types of Anticancer Agents Isolated From Plants

Jonathan L. Hartwell[1,*]

SUMMARY

The active compounds which have been isolated from plants and tested in the chemotherapy program of the National Cancer Institute since the inception of the plant program (as part of the Cancer Chemotherapy National Service Center) are listed, classified into types, and discussed in terms of their activity in experimental tumor systems. The tumor systems include the most important ones comprising the regular screen at different times and also the slow-growing tumors, B16 melanoma and Lewis lung carcinoma (new). The structure-antitumor activity relationships bring out the desirability for further investigation of certain types of compounds as possibilities for clinical trial. Notes on the current pharmacologic and clinical status of certain compounds are also presented.

[Cancer Treat Rep 60:1031–1067, 1976]

From the earliest days of the Cancer Chemotherapy National Service Center (1956) it was realized that a comprehensive program for testing compounds for antitumor activity must include those of natural as well as synthetic origin. It was also known that nature is able to produce a wide variety of chemical entities of novel structure. Many of the new and novel compounds isolated from natural sources might otherwise have never been discovered, especially those of considerable complexity requiring the development of methods for the creation of new ring systems. Natural products appeared to be a promising source for new types of compounds to test for antitumor activity. Consequently, a fermentation program was initiated in 1956 and in 1957 the plant program followed although a few plant extracts were received and tested in 1956. Procurement of animals and their extracts began in 1962.

Before the establishment of the experimental natural products program, I had conducted a survey of the literature and folklore of plants with reputed efficacy in cancer (1) and found > 3000 different species of such plants reported from all over the world. Previously, I had isolated podophyllotoxin and two other lignans from the mayapple root (*Podophyllum peltatum* L.)(2), all of which were powerfully active against Sarcoma 37 in the mouse; I undertook this survey when I learned that this plant was used by the Penobscot Indians of Maine as a treatment for what was believed to be cancer (3) and that the root of this plant was recommended for cancerous tumors in a book on materia medica and therapeutics published in 1849 (4). It is interesting to observe that several derivatives of podophyllotoxin are now in clinical trial in cancer. Although the literature and folklore can provide leads for plant collecting, it was realized that selective collecting is expensive and that, besides, this kind of input would be insufficient to maintain a large program for a long time. Therefore, a world-wide random collection program was initiated with the expectation not only of uncovering new leads for the isolation of novel compounds but also of ultimately revealing correlations between anticancer activity and botanical classification that would make collection more efficient in terms of finding active agents. The success of these considerations can be judged from this and other papers in this Symposium, as well as by the multitude of published papers already in the literature which arose from our program.

METHODS

The efficient isolation of active compounds from plants in a large program is obviously dependent upon the effectiveness of the extraction procedure

[1]Drug Research and Development Program (DR&DP), Division of Cancer Treatment (DCT), National Cancer Institute (NCI), Bethesda, Md.

[*]*Reprint requests to:* Natural Products Branch, DR&DP, DCT, NCI, Blair Bldg, Rm 4A17, 8300 Colesville Rd, National Institutes of Health, Silver Spring, Md 20910.

and the bioassay methods used to detect active plants and to guide the fractionations. I believe it is worth a short discussion of these points before taking up the compounds themselves, because variations in the methods have a profound effect on the types of compounds isolated. Beginning with necessarily arbitrary methods, some improved methods have evolved over the years based on feedback from the results obtained (these are outlined in other papers in this Symposium). For example, the original antitumor screen consisted of the three mouse tumors (Sarcoma 180, Carcinoma 755, and L1210 leukemia) deemed most able to select most of the compounds considered in 1955 to be clinically useful in man. KB cell culture was added in the latter part of 1960. Plant extracts were prepared using different methods and solvents recommended by the suppliers. After it was determined that all the active crude extracts obtained by the different methods could also be uncovered by the use of 50% aqueous ethanol, a standard procedure using this solvent was adopted by all suppliers. In 1966, the Walker 256 rat carcinoma was added to the screen to replace Sarcoma 180, Carcinoma 755, and certain other tumors after an analysis of clinical results (5) showed that 33 of 45 drugs with definite clinical activity could have been predicted by L1210 leukemia and nine of 45 by Walker 256 carcinoma. The newly constituted screen had the disadvantage, from the chemical standpoint, that the ubiquitous tannins and phytosterols were very effective against Walker 256 (as well as Sarcoma 180, Carcinoma 755, and the Lewis lung carcinoma) but not against L1210 leukemia and KB cells; many plants therefore showed activity against Walker 256 and only a very few showed activity against L1210 leukemia and KB cells. Since the tannins and phytosterols could not be developed into useful anticancer drugs (6), a great deal of effort was required to find Walker 256-active agents that were nontannin in nature. The development of a novel procedure for the nondestructive elimination of tannins from plant extracts (7) permitted fractionation of nontannin Walker 256 actives only; these and the KB actives provided the only sources of antitumor plants at this time. Walker 256 was later dropped from the screen pending feedback from the clinic on the usefulness of drugs active in Walker 256 only,

Table 1. — Activity of agents and of their plants of origin

Agent	Activity	Plant of Origin	Activity
Acer saponin F	WA	Acer negundo	SA
Bruceantin	Bl,LE,PS,KB	Brucea antidysenterica	KB
Camptothecin	LE,PS,WA,KB	Camptotheca acuminata	LE
		Nappia foetida	KB,PS,LE
Ceasalin	LE,SA,WA,KB	Caesalpinia gilliesii	SA
3-Desmethylcolchicine	Bl,PS,LE	Colchicum speciosum	KB
Ellipticine	Bl,LE,PS,WA,KB	Bleekeria coccinea	KB,LE,SA
		Ochrosia moorei	KB,CA,LE,SA
Emetine	PS,LE,KB	Cephaelis acuminata	KB
Fagaronine	PS,LE	Fagara zanthoxyloides	PS
Harringtonine	LE,PS,WA,KB	Cephalotaxus harringtonia	KB
Holacanthone	Bl,PS,KB	Holacantha emoryi	KB
Homoharringtonine	LE,PS,KB	Cephalotaxus harringtonia	KB
Indicine N-oxide	Bl,PS,LE,WA	Heliotropium indicum	WA
Lapachol	WA	Stereospermum suaveolens	WA
Maytansine	Bl,LE,PS,KB	Maytenus buchananii	KB
		Putterlickia verrucosa	KB
9-Methoxyellipticine	LE,PS,SA,KB	Bleekeria coccinea	KB,LE,SA
		Ochrosia moorei	KB,CA,LE,SA
Nitidine	LE,PS,KB	Fagara macrophylla	KB
Taxol	Bl,LE,PS,WA,KB	Taxus brevifolia	KB
Thalicarpine	LL,PS,WA,KB	Thalictrum dasycarpum	KB
Tripdiolide	LE,PS,KB	Tripterygium wilfordii	KB
Triptolide	LE,LL(new),PS,KB	Tripterygium wilfordii	KB
Tylocrebrine	CA,LE,PS,KB	Tylophora crebriflora	KB

and the more sensitive mouse P388 leukemia was substituted for L1210 leukemia. The present screen consists of P388 leukemia and KB cells and does not react to the unwanted tannins or phytosterols. In fact, KB cell culture has emerged as the principal predictor of activity for newly isolated compounds against the in vivo tumors that we consider important. This is probably because most antitumor agents are also cytotoxic, and since the KB test is more sensitive than the in vivo tests (eg, P388 and L1210 leukemias), it is able to detect cytotoxic compounds in a complex mixture such as a crude extract or fraction where in vivo activity would be obscured. In practice, a KB-active plant is fractionated until the activity is concentrated into one or a few fractions. The concentrated fractions are then tested against P388 and L1210 leukemia, and activity in one or both tumors is frequently found. A majority of the plant-derived compounds of interest, including those passing the criteria (activity in P388 and L1210 leukemias, B16 melanoma, and the new Lewis lung tumor) for further pharmacologic and clinical study were isolated from plants originally found to be active against KB cells (table 1). The latest development in the preparation of crude plant extracts for testing, which has been described elsewhere in this Symposium, is the preliminary fractionation to eliminate inactive materials and concentrate the active agents present prior to testing. This procedure results in greatly increased yields of plants active in P388 leukemia and KB cells, and produces many high priority plants for fractionation. This development, however, has not yet been in operation long enough to establish its value in producing useful compounds.

RESULTS

The results are summarized in the tables which list the active compounds along with the important tumors against which they have been tested. In many cases, results are available in our files for other less important tumors than the ones listed. The gaps in the data usually stem from a shortage of compound.

The tumor systems considered, with their activity criteria, are listed in table 2. Activity as shown in the "active" columns of the tables does not always reflect reproducible activity. Many materials were tested as suspensions which frequently led to erratic results with compounds of marginal activity. Also, the effort and expense required to obtain additional material precluded the extensive testing of compounds with initial borderline activity. These compounds for which activity has not been "confirmed" have nevertheless been included since our purpose is to show the broad activity relationships of groups of compounds, not to provide the kind of data on individual compounds required for determining whether further pharmacologic testing will be performed.

Table 2. - Tumor systems

Abbreviation	Name; host	Active response
B1	B16 melanocarcinoma; mouse	ILS 1/ $\geq$40%
CA	Adenocarcinoma 755; mouse	TWI 1/ $\geq$ 58%
HE	HeLa human carcinoma; cell culture	ED_{50} 1/ $\leq$1.0
KB	Human epidermoid carcinoma of the nasopharynx; cell culture	ED_{50} $\leq$1.0 2/
LE	Lymphoid leukemia L-1210; mouse	ILS $\geq$25%
LL	Lewis lung carcinoma; mouse	TWI $\geq$58%
LL (new)	" " " "	ILS $\geq$40%
PS	Lymphocytic leukemia P388; mouse	ILS $\geq$25% 3/
SA	Sarcoma 180; mouse	TWI $\geq$58%
WA	Walker carcinosarcoma 256; rat	TWI $\geq$58%

1. TWI (tumor weight inhibition); ILS (increase in life span); ED_{50}, dose level in μg/ml at which 50% inhibition of growth of cells in vitro is noted vs untreated controls.

2. A few compounds in the following tables have been considered active where the ED_{50} was $\leq$4.0.

3. In the following tables, activity in PS is expressed by a figure in parenthesis which is the T/C or ratio of average survival of treated animals in days to that of controls x 100. T/C = ILS + 100.

No distinction is made between marginal and high antitumor activity except against P388 leukemia. In this case, the figure in parentheses after "PS" is the highest T/C obtained in any test and does provide a measure of the degree (marginal, high, or intermediate) of activity; this figure is provided because in practice so much depends on the interest generated by the first in vivo tests. While a T/C of 125% is an indication of activity, a figure of 175% is normally required for a priority high enough to warrant advanced screening and preclinical evaluation.

In the tables presented in this paper the source (table 3) of the compounds is acknowledged after the compound name. The classification adopted for the compounds listed therein is given in table 4. Broadly, all of the classes are non-nitrogenous except for the ansa macrolides, the proteins, and the alkaloids; the miscellaneous group is mixed.

Table 3. - Acknowledgments

1.	Dr. J. L. Beal	Ohio State University
2.	Dr. Jack R. Cole	University of Arizona
3.	Commonwealth Scientific and Industrial Research Organization	Melbourne, Australia
4.	Dr. M. L. Dhar	Central Drug Research Institute, India
5.	Dr. R. W. Doskotch	Ohio State University
6.	Dr. N. R. Farnsworth	University of Illinois
7.	Mr. Martin Jacobson	U.S. Department of Agriculture
8.	Dr. G. J. Kapadia	Howard University
9.	Dr. L. H. Kier	Massachusetts College of Pharmacy
10.	Dr. D. G. I. Kingston	Virginia Polytechnic Institute
11.	Dr. S. Morris Kupchan	University of Virginia
12.	Dr. G. R. Pettit	Arizona State University
13.	Charles Pfizer and Co., Inc.	Maywood, N.J.
14.	Mr. R. G. Powell	U.S. Department of Agriculture
15.	Dr. B. Prescott	National Institute of Allergy and Infectious Diseases
16.	Dr. M. Silva	University of Concepcion, Chile
17.	Dr. Monroe E. Wall	Research Triangle Institute
18.	Dr. E. Gellert	Wollongong University College
19.	Dr. J. M. Cassady	Purdue University
20.	Dr. Ming-Lu King	National Defense Medical Center, Taiwan
21.	Dr. A. C. Casey	Stauffer Chemical Company
22.	Dr. D. H. Miles	Mississippi State University
23.	Dr. F. C. Chang	University of Tennessee
24.	Dr. G. J. Persinos	Bergstrom Toxicology Laboratory

Table 4. - Classification

Tannins
Sterols (incl. simple glycosides; excl. saponins)
Quinones (incl. quinoids and quinols)
Terpenes
Iridoids
Sesquiterpenes
Diterpenes
Tripterpenes (incl. cucurbitacins; excl. saponins)
Lignans
Flavonoids
Saponins and their aglycones
Steroidal
Triterpenoid
Steroid lactones (incl. cardenolides, bufadienolides, withanolides and their aglycones)
Quassinoids (simaroubolides)
Ansa macrolides
Proteins
Alkaloids
Miscellaneous

Tannins

No formal attempts were made to prepare pure compounds from this heterogeneous group of widely occurring polymeric materials after it was shown that the tannin fractions were generally inactive against the predictive tumors (L1210 and P388 leukemias and KB cells), were active against uninteresting tumors (Carcinoma 755, Lewis lung, Sarcoma 180, and Walker 256), and were quite toxic. Moreover, they were generally chemically unstable, being susceptible to air oxidation and further polymerization.

In 1969 (6), 82 different active plant species were listed as owing their activity solely to tannins. Since that time, another 82 species have been similarly identified. Fortunately, the makeup of the current screen precludes the appearance of more plants whose activity is due to tannins.

Sterols (Including Simple Glycosides but Excluding Saponins)

The phytosterols and their glycosides are widely distributed in plants. The ones that have shown antitumor activity are given in table 5. Only daucosterol showed marginal activity in P388 leukemia. Other phytosterols such as cholesterol (NSC-8798), ergosterol (NSC-62791), and stigmasterol (NSC-8095) have been tested in a variety of tumors (6), including Carcinoma 755, L1210 leukemia, Sarcoma 180, and Walker 256, without showing activity; in addition, stigmasterol was inactive in P388 leukemia and ergosterol was inactive in KB cells.

In 1969 (6), 20 different active plants were listed as owing their activity to sterols (mostly β-sitosterol), and since then, another 42 species have appeared. Again, the antitumor screen eliminates most of the plants whose activity is due to sterols.

Quinones (Including Quinoids and Quinols)

Table 6 lists the quinones that have shown antitumor activity. Although some activity has been ob-

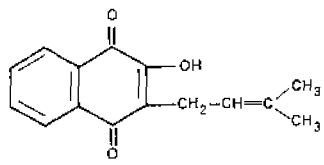
Table 5. - Sterols

	NSC	Active	Inactive
Daucosterol 16/ (β-sitosterol glucoside)	165962	PS(134)	LE, KB
β-Sitosterol	8096	CA, LL, WA	B1, LE, LL(new) SA, KB
	18173		
	49083		
	86199		

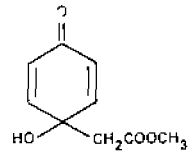
Table 4. -- Quinones

	NSC	Active	Inactive
Alkannin 4/	94524	WA	LE,PS,SA,KB
Alkannin β,β -dimethylacrylate 4/	140377	PS(136),WA	B1,LE
Alkannin monoacetate 4/	140376	WA	
Emodin (aloe-emodin) 11, 16/	38628	PS(127),WA	CA,LE,SA,KB
Jacaranone 6/	251682	PS(165),KB	
Lapachol 13/	11905	WA	B1,CA,LE,LL, LL(new),PS, SA,KB
Taxodione 11/	122419	WA,KB	LE,PS
Taxodone 11/	122420	KB	

QUINONES



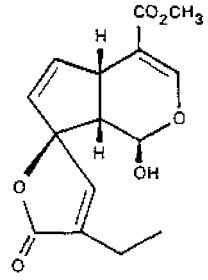
Lapachol
NSC-11905



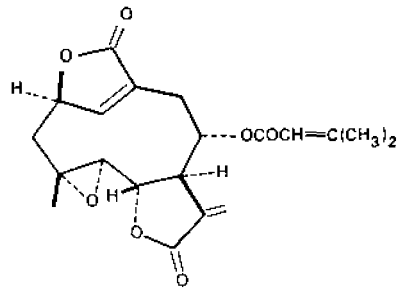
Jacaranone
NSC-251682

FIGURE 1

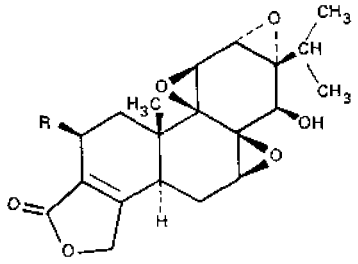
TERPENES



Allamandin
NSC-251690

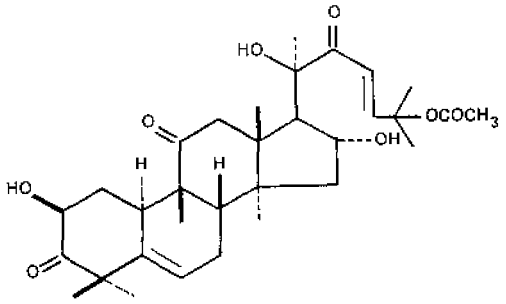


Elephantopin
NSC-100046



Triptolide
NSC-163062 R = H

Tripdiolide
NSC-163063 R = OH



Cucurbitacin B
NSC-49451

FIGURE 2

tained against P388 leukemia (the best is jacaranone),[2] no activity has been found against L1210 leukemia, B16 melanoma, or Lewis lung carcinoma, and this class of compounds cannot presently be considered very promising. Lapachol (fig 1), originally obtained from *Stereospermum suaveolens* (Roxb.) DC., has been carried into clinical trial mostly on the basis of its high Walker 256 activity even when given orally (8). Lack of toxicity permitted large oral doses but sufficiently high blood levels could not be obtained to show a therapeutic effect.

It is perhaps of passing interest that *Tabebuia* and *Tecoma* species, containing lapachol, have long been popularly used in Brazil for cancer and that a *Jacaranda* species, called cancer bush, is popularly used in the Bahamas for skin cancer (1).

[2]Farnsworth NR. Personal communication.

Terpenes

This large and complex group of natural products has proved to be of substantial interest to us. The natural breakdown into chemical subgroups reveals that only the iridoids, sesquiterpenes, diterpenes, and triterpenes have antitumor activity. No activity has been found among the monoterpenes, sesterterpenes, and carotenoids. Figure 2 gives representative examples of the chemical structures of these active classes, namely, an iridoid (allamandin), a sesquiterpene (elephantopin), two diterpenes (triptolide and tripdiolide), and a triterpene (cucurbitacin B). Allamandin was obtained from *Allamanda cathartica* L. (9), elephantopin from *Elephantopus elatus* Bertol. (10), triptolide and tripdiolide from *Tripterygium wilfordii* Hook. fil. (11), and cucurbitacin B from several sources not all Cucurbitaceae—*Cucurbita digitata* Gray,[3] *Luffa graveolens* Roxb.,[4] *Begonia* X *tuberhybrida* Voss (12), and *Datisca glomerata* (Presl) Baill.[5]

a. Iridoids.—Table 7 lists the active iridoids (all of which are lactones) which have been isolated to date. Lack of material has prevented testing in a wider variety of tumors but it is encouraging that at least some P388 leukemia activity has been shown by two of the four substances.

Table 7. – Iridoids

	NSC	Active	Inactive
Allamandicin 11/	251691	PS in vitro	PS,KB
Allamandin 11/	251690	PS(145),KB	
Isoplumericine 11/	112153	PS in vitro	LE
		PS(145),KB	
Plumericine 11/	112152	KB	LE

b. Sesquiterpenes.—Table 8 shows the active sesquiterpenes that have been isolated in the fractionation program. All but one are lactones. Many more have been received and tested in the "synthetic" program but the results obtained do not generally alter the comments made here. A majority (38 of 47) of the compounds have cytotoxic activity (KB or P388 leukemia in vitro), a few (eight of 47) have activity against Walker 256, and a large number (23 of 47) showed activity against in vivo P388 leukemia. A sufficient number of P388 leukemia actives have relatively high T/Cs for some interest to be maintained in this subgroup. Although none has shown activity as yet in L1210 leukemia or in either of the two slow-growing tumors, B16 melanoma and Lewis lung (new), hope remains that additional testing will reveal such activity. There is some evidence that certain chemically reactive functional groups besides the lactone group (α, β-unsaturated carbonyl, epoxy) are important for in vivo antitumor activity and that polyfunctionality seems to increase the chances for activity. However, physico-chemical and steric factors are undoubtedly important also, and the whole question of structure-activity relationships is in need of clarification.

c. Diterpenes.—This subgroup (table 9) has yielded two compounds of high activity in P388 leukemia. Two others, triptolide and tripdiolide, are also active in L1210, and tripdiolide is active against the Lewis lung carcinoma. Additional studies will be performed on the latter two compounds as more plant material becomes available.

d. Triterpenes (excluding saponins).—This group so far has not been promising. The cucurbitacins as a class (table 10) show general cytotoxicity and negative or marginal in vivo antitumor activity against P388 leukemia, L1210 leukemia, B16 melanoma, and Lewis lung tumor (new). Our present screen will continue to identify plants containing

Table 8. – Sesquiterpenes a/

	NSC	Active	Inactive
Ambrosin 2/	85235	PS(180),KB	SA,LE
Arctiopicrine 2/	177853	PS(140),KB	
Artemisiifolin 2/	177852	PS(130),KB	
Baileyin 12/	179192	PS in vitro	
Costunolide 2,5/	106404	KB	LE,WM
Damsin 5/	85249	KB	LE
Elephantin 11/	102817	WA,KB	LE
Elephantopin 11/	100046	WA,PS(160)	LE,LL,SA
10-Epieupatoroxin 11/	135068	KB	
Epitulipinolide 5/	142844	KB	
Erioflorin 11/	144151	PS(127),KB	LE
Erioflorin acetate 16/	251667	PS(131),KB	
Erioflorin methacrylate 16/	251666	KB	PS
Eriolangin 11/	182855	PS(128)	KB
Eriolanin 11/	144152	PS(152),KB	
Eupachlorin 11/	114567	KB	WA
Eupachlorin acetate 11/	114568	WA,PS(155), KB	
Eupachloroxin 11/	114570	KB	
Eupacunin 11/	135020	WA,PS(135), KB	
Eupacunoxin 11/	135021	KB	
Euparotin 11/	104942	KB	
Euparotin acetate 11/	104943	WA, KB	PS
Eupatocunin 11/	135023	KB	
Eupatofolin 11/	135023	PS (150), KB	
Eupatoroxin 11/	114569	KB	
Eupatundin 11/	114566	PS (133), KB	LL, LE, SA, WA

[3]Cole JR. Personal communication.
[4]Dhar ML. Personal communication.
[5]Kupchan SM. Personal communication.

Table 8. – Sesquiterpenes a/ (continued)

	NSC	Active	Inactive
Fastigilin B 12/	176503	PS (137)	Bl, LE, LL(new), KB
Fastigilin C 12/	176507	PS (137)	KB
Gaillardin 11/	106394	KB	LE
Helenalin 12,17/	85236	PS (220), KB	Bl, LE, LL, LL(new), SA, WA
Helenalin acetate 17/	166124	PS (165)	
Isogaillardin 11/	106395	KB	
Liatrin 11/	135034	PS (163)	
Lipiferolide 5/	251676	KB	
Nardol diastereomer (?) b,13/	127084	WA	
Ovatifolin acetate 16/	--	PS (143), KB	
Parthenolide 2/	157035	KB	PS, LE
Paucin c,2/	136722	PS (138)	Bl, LE
Tulipinolide 5/	106405	KB	LE, WA
Vernodalin 11/	124459	WA, KB	
Vernolepin 11/	106398	WA, PS (145), KB	
Vernolide 11/	124460	KB	WA, LE, PS
Vernomenin 11/	116070	PS (136)	KB
Vernomygdin 11/	135072	KB	
Zaluzanin C 2/	177851	PS in vitro	PS
from Acanthospermum 6/	--	PS (147), KB	
" Centaurea 2/	--	PS (150), KB	

a/ All lactones except the one noted.

b/ Not a lactone.

c/ A glycoside.

these compounds because of their KB cell activity. The remaining triterpenes (table 11) which have been isolated are generally not cytotoxic but show activity in Walker 256. Negative or marginal in vivo antitumor activity against the P388 and L1210 leukemias, and against the slow-growing tumors, has made this group of little interest for our program.

Lignans

These are a group of rather uncommon plant constituents which are found in some plants with activity against KB cells. The chemical skeletons of the group are shown in figure 3. The bisbenzocyclooctadiene skeleton on the right is a type recently added to the classic lignan family. Although podophyllotoxin (fig 3) never passed our criteria for pharmacologic and clinical study, several semisynthetic relatives have been in clinical trial here and elsewhere in the world (13). Two of them, VM-26 and VP-16-213, have produced responses in brain tumors, lymphosarcomas, and (in Europe) Hodgkin's

Table 9. – Diterpenes

	NSC	Active	Inactive
Gnidicin 11/	238941	PS (173)	
Gnididin 11/	238942	PS (127)	
Gniditrin 11/	238943	PS (168)	
12-Hydroxydaphnetoxin 11/	239073	PS (131)	
Jatrophone 11/	135037	PS (145), KB	Bl, LE, LL, LL(new)
Nozeredn 11/	239072	PS (200)	Bl, LL(new)
Podolide 11/	238978	KB	PS
Taxodione (also under Quinones) 11/	122419	WA, KB	LE, PS
Taxodone " " " 11/	122420	KB	
Tripdiolide 11/	163063	LE, PS (158), KB	Bl, LL(new)
Triptolide 11/	163062	LE, LL(new), PS (131), KB	Bl
Triptonide 11/	165677	KB	LE
from Jatropha	--	PS (141)	

Table 10. – Cucurbitacins

	NSC	Active	Inactive
Cucurbitacin B 2,4,5,11/	49451	PS (135), KB	Bl, CA, LE, LL, SA, WA
" D 5,11,16/	521776	PS (131), KB	LE, WA
" E 11,17/	106399, 521775	LL, KB	Bl, LE, PS, SA, WA
" F 11/	--	WA, KB	LE, PS
" I 11/	521777	KB	LE, PS, WA
" L 2/	112167	PS in vitro, KB	PS, WA
" P 11/	135074	KB	
" Q 11/	135075	KB	
a Cucurbitacin glycoside 11/	--	KB	
" " " 11/	--	KB	
" " " 11/	--	KB	
" " " 11/	--	KB	
Datiscacin (Cucurbitacin R) 11/	144154	KB	
Datiscoside (Cucurbitacin D dehydroepirhamnoside) 11/	144153	LL, PS (150), WA, KB	Bl, LE, LL(new)
Dihydrocucurbitacin B 5,11/	106401	KB	WA
Isocucurbitacin B 11/ (2-Epicucurbitacin B)	106400	KB	

disease. These compounds differ from podophyllotoxin in that they are demethylated at the 4′ position, are epimerized at the 1 position, have a glucoside on the 1-hydroxyl group, and are acetals by reaction with aldehydes. The original 4′-demethylpodophyllotoxin came from *Podophyllum hexandrum* Royle [*P. emodi* Wall. ex Royle]. Table 12 lists the active lignans isolated during fractionation.

While several of the compounds have shown high activity in P388 leukemia, they have not met the other criteria required to justify further study.

Table 11. - Triterpenes

	NSC	Active	Inactive
α-Amyrin 2,4/	114787	WA	Bl, LL(new) PS, KB
Betulin 2/	4644	WA	Bl, CA, LE, LL, SA, WA
Betulinic acid 2,22/	113090	PS (140), WA	KB
Lupeol 2,21/	90487	WA	LE, PS, SA, KB
Ursolic acid 2,6,17/	4060	PS (125)	Bl, LE, LL(new), WA, KB
Uvaol 2/	159627	PS (125)	
from Bursera 2/	--	WA	
" Jatropha 2/	--	PS (158)	
" Maytenus 6/	--	PS (166), KB	
" Rubia 2/	--	WA	

Table 12. - Lignans

	NSC	Active	Inactive
Burseran 2/	123428	WA, KB	
Dehydroanhydropicropodophyllin 2/	--	PS in vitro	
3'-Demethylpodophyllotoxin 6/	251681	PS (130), KB	
Deoxypodophyllotoxin 2,6,11,17,23/	403148	LE, PS (154), KB	Bl, LL, LL(new), SA, WA
5'-Desmethoxy-β-peltatin A methyl ether 2/	126727	PS (189), WA, KB	Bl, LE
(+)-Dimethylisolariciresinol-2α-xyloside 11/	--	KB	PS, WA
Justicidin B 11/	254665	KB	
α-Peltatin 17/	24817, 35463	PS (140), KB, LE	Bl, CA, LL, LL(new), SA, WA
β-Peltatin 17/	24819, 35471	PS (168), WA, KB	Bl, LE, LL(new), SA
β-Peltatin A methyl ether 2/	126726	PS (172), WA	
Podophyllotoxin 6,11,23/	24818	PS (171), WA, KB	Bl, CA, LE, LL, LL(new), SA
Podophyllotoxin glucoside 9/	163024	KB	
Steganacin 11/	172958	PS (140), KB	LE
Steganangin 11/	172956	KB	LE, PS
Steganol 11/	172959	KB	PS
Steganone 11/	172957	KB	PS

Flavonoids

This very common class of plant constituents is generally inactive in our antitumor screen. Many have been submitted as "synthetics." Table 13 lists those showing activity during fractionation. Only one showed marginal activity in P388 leukemia.

Table 13. - Flavonoids

	NSC	Active	Inactive
Centaureidin 11/	106969	KB	PS
Taxifolin 16/	36398	PS (142)	LE, SA
3',5,7-Trihydroxy-3,4'-dimethoxyflavone 11/	106970	KB	PS

Table 14. - Saponins

Steroidal	NSC	Active	Inactive
Myrsine saponin 6,11/	123126	WA	
from Agave 2/	--	WA	
" " 2/	137440	WA	PS
" " 2/	--	WA	
" " 2/	--	WA	
" Hesperaloe 17/	--	WA	
" Solanum 17/	--	WA	
" Trillium 17/	--	WA	
Triterpenoid			
Acer saponin P 11/	100045	WA	Bl, LE, LL LL(new), PS, KB
" " Q 11/	123429	SA	WA
Celsioside C 4/	173116	WA	LE, KB
from Acer 17/	--	WA, PS (141)	
" Entada 13/	115727	WA, LL	LE, PS, Bl
" Ipomopsis 17/	--	WA	
" Machaeranthera 17/	--	PS (129)	WA
Undetermined			
from Agave 11/	--	LL	
" " 11/	--	SA	
from Agave 17/	--	WA	
" Allium 11/	--	SA	
" Aster 6/	--	WA	PS
" " 17/	--	WA, PS (135)	
from Chrysopsis 11/	--	SA	
" Cyclamen 11/	135029	WA	KB
" Saponaria 13/	77472	WA, SA	CA, LL, LE, PS

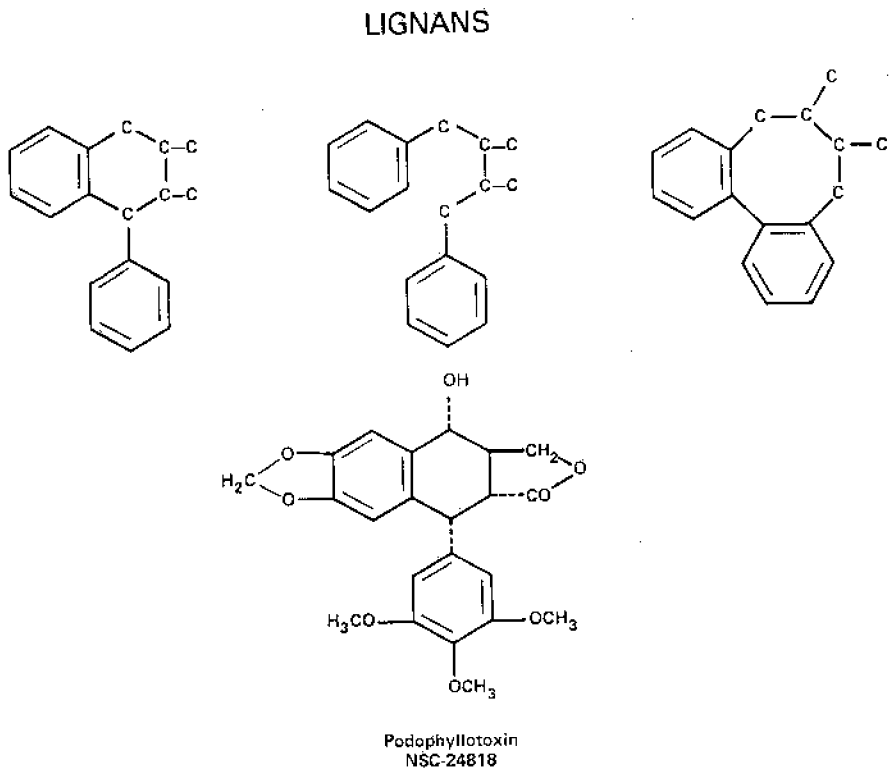
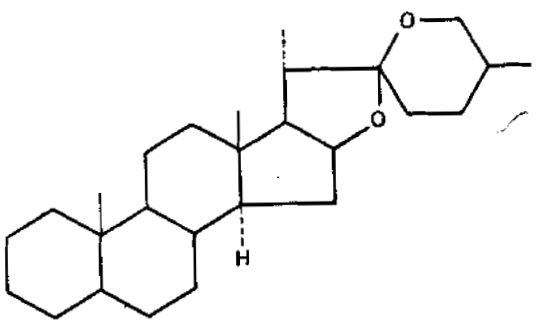


FIGURE 3

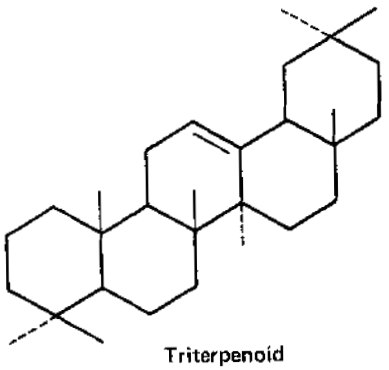
Saponins

This widely disseminated class of plant constituents generally possesses activity against Walker 256 and Sarcoma 180, but lacks activity in KB cells. Twenty-three new active saponins have been added to the ten that were listed in 1969 (6); although isolated in some state of purity, in many cases the nature of the aglycone is undetermined (table 14). They have shown marginal activity against P388 leukemia, and no activity against L1210 leukemia or the slow-growing tumors. Thus, plants whose antitumor activity is attributable to saponins will probably not be detected with our current screen. Nevertheless, since they are so widespread in the plant kingdom, and since many were active in Walker 256, it was decided to continue studies on the best one, Acer saponin P, in order to obtain feedback. Figure 4 gives the carbon skeletons of the two main types of saponins, steroidal and triterpenoid, and the partial formula for Acer saponin P. This substance was obtained from *Acer negundo* L. (14) and is now being prepared in quantities sufficient for pharmacologic and clinical trials.

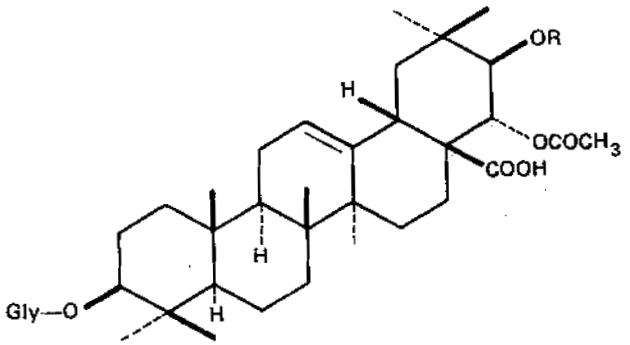
SAPONINS



Steroidal



Triterpenoid



R = Mixture of $-CO(CH\underset{t}{=}CH)_2CH(CH_3)CH_2CH_3$ and

$-CO(CH\underset{c}{=}CH)CH\underset{t}{=}CH)CH(CH_3)CH_2CH_3$

Acer saponin P
NSC-100045

FIGURE 4

Steroid Lactones (Including Cardenolides, Withanolides, Bufodienolides, and Their Aglycones)

The carbon skeletons of these three types of lactones are given in figure 5. The cardenolides, especially, are widely distributed in nature. Table 15 lists the active steroid lactones isolated during fractionation; the type of lactone is indicated in the first column. It is apparent that they are generally cytotoxic with very little activity in any in vivo tumors. Plants containing these compounds will show up in our screen but will be ruled out, for the most part, when KB-active concentrates are subjected to P388 and L1210 leukemia testing.

Quassinoids (Simaroubolides)

This group of bitter plant principles has proved to be of great interest. Figure 6 presents the formulas of the two most promising representatives. Bruceantin was isolated from *Brucea antidysenterica* J.F. Mill. (15), a plant used in Ethiopia and Eritrea for cancer (1), and holacanthone from *Holacantha emoryi* Gray (16). Table 16 outlines data on the active compounds which have been isolated. In general, they are cytotoxic; a large proportion of them are highly active in P388 leukemia and several are also active in L1210 leukemia or B16 melanoma. It is evident that plants containing active quassinoids will be readily detected by our screen. Bruceantin is

Table 15. - Steroid lactones and their aglycones

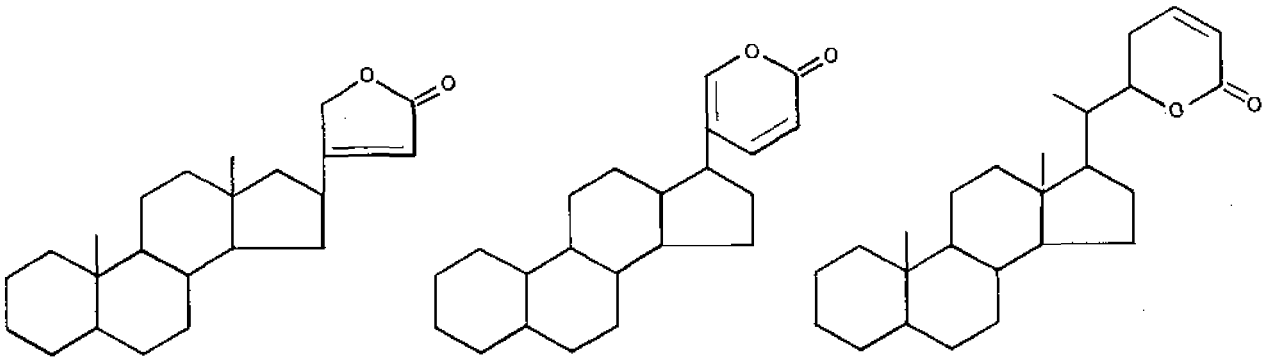
Type a/	Name	NSC	Active	Inactive
C,G	Acobioside A 8/	116788	KB	
C,G	Acolongifloroside K 10/	152149, 173717	KB	LE
C,G	Acospectoside A 8/	113569	KB	LE
C,G	Acovenoside A 6,10/	116787	KB	Bl, LE, PS
C,G	Acovenoside B 8/	116789	KB	
C,G	Adynerin 2/	251673	KB	Bl, LL(new) PS in vitro
C,G	Apocannoside 11/	83216	KB	LE, PS, SA, WA
B,A	Bersaldegenin 3-acetate 11/	135076	WA, KB	
B,A	Bersaldegenin 1,3,5-orthoacetate 11/	135077	KB	
B,A	Bersamagenin 1,3,5-orthoacetate 11/	135032	KB	
B,A	Bersecillogenin 11/	--	KB	
B,A	Bersenogenin 11/	251692	KB	
C,G	Calotropin 11/	143925, 106393	KB	LE
C,G	Cerberin 2/	251674	PS (130), KB	
C,A	Coroglaucigenin 11/	144150	KB	
C,G	Cymarin 6,11/	7522	KB	CA, LE, LL PS, SA, WA
C,G	Desglucouzarin 6/	--	KB	LE, PS
C,G	Digitoxin 14/	7529	KB	CA, LE, PS, SA, WA
B,A	3-Epibersecillogenin 11/	135067	KB	
C,A	Gitoxigenin 5/	407807	KB	
B,A	Hellebrigenin 3-acetate 11/ (Bufotalidin acetate)	106676	WA, KB	
B,A	Hellebrigenin 3,5-diacetate 11/	109330	KB	WA

Table 15. - Steroid lactones and their aglycones (continued)

Type a/	Name	NSC	Active	Inactive
B,A	16β-Hydroxybersaldegenin 1-acetate 11/	135080	KB	
B,A	16β-Hydroxybersaldegenin 3-acetate 11/	135079	KB	
B,A	16β-Hydroxybersaldegenin 1,3,5-orthoacetate 11/	135078	KB	
B,A	16β-Hydroxybersamagenin 1,3,5-orthoacetate 11/	251695	KB	
C,G	Hyrcanoside 10/	--	PS (133), KB	
C,G	Neriifolin 2/	123976	LL, SA, KB	LE, PS, WA
C,A	Oleandrigenin 5/	148790	KB	LE
C,G	Oleandrin 2/	93089	KB	LE, WA
C,G	Opposide 10/	173716	KB	
C,A	16-Propionylgitoxigenin 5/	160843	KB	
C,G	Rhodexin B 5/	160845	KB	
B,A	Scilliglaucosidin 11/	135036	KB	PS
C,G	Somalin 2/	251698	KB	PS
C,A	Strophanthidin 6/	86078	KB	Bl, LE, LL(new), PS
C,A	Uzarigenin 11/	119993	KB	PS, WA
W,A	Withacnistin 11/	135073	KB, WA	
W,A	Withaferin A 11,17/	101088	PS (135), SA WA, KB	
C,G	from Asclepias 6/	--	PS (150), KB	LE
C(?),G	" Crossosoma 2/	--	KB	
--	" Elaeodendron 11/	--	KB	

a/ Symbols: B=bufodienolide, C=cardenolide, W=withanolide, A=aglycone, G=glycoside

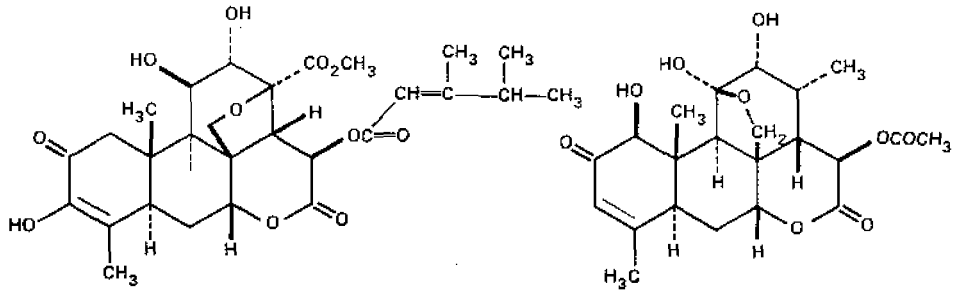
STEROID LACTONES



Cardenolides | Bufadienolides | Withanolides

FIGURE 5

QUASSINOIDS



Bruceantin
NSC-165563

Holacanthone
NSC-126765

FIGURE 6

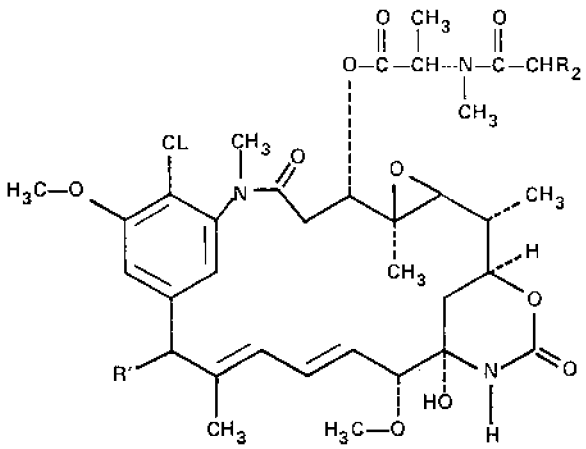
now being prepared in quantities sufficient for toxicologic and pharmacologic studies.

Ansa Macrolides

This is a relatively new class of compounds characterized chemically by the presence of a large macrocyclic lactone ring, frequently *N*-heterocyclic, and incorporating within it an *m*- or *p*-bridged aromatic moiety. The class was originally found among microbial products and the current findings represent their first appearance in higher plants. Figure 7 gives the formula for two representative members and table 17 lists the ones isolated so far in fractionation. Maytansine was isolated from several *Maytenus* species (17) and colubrinol from *Colubrina texensis* (Torr. & Gray) Gray (18). The group is generally cytotoxic and is unusually active in P388 leukemia at remarkably low doses. Maytansine, the most readily available member of the group, is also active in L1210 leukemia and B16 melanoma and is now in clinical trial. It is interesting to note that one of the *Maytenus* species, many of which are known to contain maytansine, has been in popular use for 30 years in South Africa in an herbal mixture for carcinoma and sarcoma.

Proteins

Over the years, proteinaceous materials have been isolated as the active agents in several plants (table 18). Some were thought to be simple proteins



Maytansine NSC-153858 R = R' = H

Colubrinol NSC-196519 R = CH_3; R' = OH

FIGURE 7

Table 16. - Quassinoids

	NSC	Active	Inactive
2'-Acetylglaucarubinone 11/	194251	PS (157), KB	
Aflanthinone 11/	238187	PS (148), KB	
Bruceantarin 11/	175399	PS (150), KB	
Bruceantin 11/	165563	B1, LE, PS (220), KB	LL(new)
Bruceantinol 11/	238177	LE, PS (145), KB	
Bruceine B 11/	132793	PS (130), KB	
Dehydroailanthinone 11/	238188	PS (184), KB	
Dehydrobruceantarin 11/	238179	PS (133), KB	
Dehydrobruceantin 11/	238178	PS (135)	KB
Dehydrobruceantol 11/	238180	KB	
Glaucarubinone 11,17/	132791	B1, PS (231), KB	LE, LL(new)
Glaucarubolone 11,17/	238189 126764	PS (150), KB	LE
Holacanthone 17/	126765	B1, PS (127), KB	LE, WA
Isobruceine B 11/	238181	PS (140), KB	LE

Table 17. - Ansa macrolides

	NSC	Active	Inactive
Colubrinol 17/	196519	PS (213), KB	
Colubrinol acetate 17/	196520	PS (206), KB	
Maysenine 11/	219974	KB	PS
Maysine 11/	219972	KB	PS
Maytanacine 11/	239387	PS (190), KB	
Maytanbutine 11,17/	165014	PS (190), KB	
Maytanprine 11/	165013	PS (161)	
Maytansine 11/	153858	B1, LE, PS (220), KB	LL(new)
Maytansinol 11/	239386	KB	
Maytanvaline 11/	219970	PS (201), KB	
Normaysine 11/	219973	KB	PS

Table 18. - Proteins

	NSC	Active	Inactive
Simple proteins (?)			
from Caesalpinia 2/	--	SA	
" Cerastium 2/	--	SA	
" Cercidium 2/	--	LL, WA	
" Gutierrezia 2/	--	SA	
" Mertensia 2/	--	SA	
Glycoproteins (?)			
Cesalin 2/	110435	LL, SA, WA, KB	B1, PS, LE, LL(new)
from Mirabilis 2/	--	LL, SA, WA	
" Muscari 15/	--	WA	
" Osteomeles 2/	--	SA	

and others were thought to be glycoproteins but, with one exception, they were never purified. The one with the highest activity in Walker 256, obtained from *Caesalpinia gilliesii* (Hook.) D. Dietr. in good yield (19), was selected for further development. Purification yielded a product (named cesalin), highly active in Walker 256 but inactive in the leukemias and slow-growing tumors, B16 melanoma and Lewis lung carcinoma (new). As a representative of a large class of natural products, it will be interesting to follow its progress in preclinical pharmacologic and possible clinical trials.

Alkaloids

More members of this class of compounds have come out of the plant fractionation program than of any other class. They are widely distributed in the plant kingdom and many are active against KB cells or Walker 256 carcinoma. After isolation, activity in other in vivo tumor systems has frequently been found. The great diversity of chemical types in this group of compounds is illustrated in table 19 which lists the classes into which the 80 isolated alkaloids (table 20) fall. No attempt will be made to draw any structure-activity relationships since the number of compounds is too small and the data are too scanty. Rather, a few of the alkaloids that have proved to be most interesting will be discussed. Figures 8–12 represent most of the interesting alkaloids in our program and typify the variety of the chemical structures encountered, some of which are novel.

Table 19. - Alkaloids

Class			
1.	Aliphatics	14.	Amaryllidaceae alkaloids
2.	Colchicine group	15.	Canthine group
3.	Pyrrolizidines	16.	Rauvolfia alkaloids
4.	Tetrahydroisoquinolines	17.	Isoquinuclidines
5.	Bisbenzylisoquinolines	18.	Dimeric indoles
6.	Aporphines	19.	Ellipticine group
7.	Dibenzopyrrocolines	20.	Taxanes
8.	Morphinane group	21.	Camptothecin group
9.	Protoberberines	22.	Furoquinolines
10.	Benzophenanthridines	23.	Sterol alkaloids
11.	Emetine group	24.	Cephalotaxus alkaloids
12.	Alangium alkaloids	25.	Amopterus alkaloids
13.	Phenanthroquinolizidines and phenanthroindolizidines	26.	Alkaloids of unknown structure

a. Thalicarpine (fig 8).—This is the first dimeric alkaloid recognized to contain both the aporphine and benzylisoquinoline moieties (20). It entered clinical trial primarily on the basis of its Walker 256 antitumor activity. Major organ toxicity is consistently manageable. While it is still under study in the clinic, however, its prospects do not look promising.

b. Indicine N-oxide (fig 8).—Many pyrrolizidine alkaloids have been tested besides the four reported here (6), but indicine *N*-oxide, from *Heliotropium indicum* L., is the only one possessing significant activity in P388 leukemia. Since it is also active against the B16 melanoma, L1210 leukemia, and Walker 256, it was entered into clinical trials. Although pharmacologic testing is as yet incomplete, negative histopathologic findings indicate that the hepatotoxicity commonly associated with this class of alkaloids may not be a clinical problem with this compound.

Heliotropium indicum has been used since ancient times against warts and its close relative, *H. europaeum* L., has been recommended for cancer treatment (1).

c. Camptothecin (fig 9).—This novel structure, isolated in minute quantity from the wood of *Camptotheca acuminata* Decne. (21), is highly active in P388 and L1210 leukemias but causes gastrointestinal tract toxicity in the mouse. Results from its first clinical trial in patients with gastrointestinal cancer looked very promising (22), but subsequent work did not uphold the earlier findings.

Camptothecin is present in the plants along with smaller quantities of the 10-hydroxy and 10-methoxy derivatives (23). Since these also have high activity in P388 and/or L1210 leukemias it is possible that one of them might yield better clinical results. Accordingly, a comparative advanced bioassay is being carried out on camptothecin, the two derivatives, and 9-methoxycamptothecin in order to provide a basis on which to select one for further development.

It is interesting that a plant not closely related, *Mappia foetida* (Wight) Miers, has yielded both camptothecin and 9-methoxycamptothecin (24); preliminary tests with the latter compound reveal activity similar to the 10-methoxy derivative.

d. Taxol (fig 9).—This novel compound was isolated from *Taxus brevifolia* Nutt. and other *T.* species (25). Because of its high activity in the tumors of interest, suitably large quantities are being prepared for further study.

e. Ellipticine (fig 10).—Ellipticine and its 9-methoxy derivative were isolated from *Excavatia coccinea* (Teysm. & Binnend.) Markgraf and *Ochrosia moorei* (F. Muell.) F. Muell. (26). Their high activity in the leukemias indicated the further development of one of them. Ellipticine was selected because of better activity by the oral route and better availability by large-scale synthesis. Pharmacologic studies of this compound are in progress, and clinical studies of the 9-methoxy derivative have been carried out in France (27).

f. Tylocrebrine (fig 10).—This alkaloid, obtained from *Tylophora crebriflora* S.T. Blake (28), has been through limited clinical trial. Irreversible and unmanageable central nervous system effects, not anticipated from preclinical work, precluded further clinical studies.

g. Nitidine and fagaronine (fig 10).—These closely related alkaloids, isolated from *Fagara macrophylla* (Oliv.) Engl. (29) and *F. zanthoxyloides* Lam. (30), respectively, showed activity in the Lewis lung

Table 20. – Alkaloids

	Class b/	NSC	Active	Inactive
Anopterine a,3/	25	179172	KB	WA, LE
Berberine sulfate 1,4,11,17,20/	9	5359	Bl, PS (131), KB	SA, LE, WA
				CA, LL, LL(new)
Camptothecin 4/17/	21	94600	LE, PS (250), WA, KB	
Chelidimerine 6/	10	--	KB	
Corsulinine 6/	5	--	KB	
Colchicine 11/	2	757	PS (191), WA, LE, KB	Bl, CA, LL LL(new), SA
Compound from Alangium 13/	26	92071	SA, WA, PS (126)	CA, LE
" " " 17/	26	--	CA, KB	
" " Dichroa 17/	26	--	PS (165), KB	
Compound B from Tylophora crebriflora 13/	13	85707	CA, LE	SA, WA
" C " " 13/13		85706	CA, LE, SA, WA	
" D " " 13/13		85709	LE, PS (177)	
" E " " 13/13		92070	WA	CA, LE, SA
Compound D from Tylophora indica 13/	13	100056	HE	LE
" E " " 13/	13	100057	HE	LE
Conessine hydrochloride 6/	23	32989	WA, KB	CA, LE, SA
Coptisine chloride 6/	9	119754	KB	
Crinamine 3/	14	88421	KB	
Cryptopleurine 6/	13	19512	KB	CA, LL, SA, Bl, LE, PS, W
Cryptowolline iodide 3/	7	86342	KB	
Cycleadrine 11/	5	--	KB	
Cycleamorine 11/	5	--	KB	WA
Cycleapeltine 11/	5	--	KB	WA
Cycloprotobuxine 11/	23	102244	WA, PS (145)	
Demecolcine 11/	2	3096	PS (150), WA	Bl, CA, LL
		403147	LE, KB	LL(new), SA
3-Desmethylcolchicine 11/	2	172946	Bl, PS (236), LE	LL(new)
Desmethyltylophorinine 13/	13	94739	LE, PS (146)	
(-)-Dicentrine 11/	6	--	KB	PS
Ellipticine 3/	19	71795	WA, LE, Bl PS (208), KB	LL(new)
Emetine hydrochloride 17/	11	33669	PS (232), LE, KB	Bl, CA, LL, SA, WA
Fagaronine 6/	10	157995	PS (270), LE	Bl, KB
N-Formyldesacetylcolchicine 11/	2	403142	LE, PS (190), WA, KB	Bl, CA, LL(new), SA

Table 20. – Alkaloids (continued)

	Class	NSC	Active	Inactive
Harringtonine 14,17/	24	124147	LE, PS (304, NA, KB	Bl, LL(new)
Homoharringtonine 14/	24	141633	LE, PS (309), KB	Bl, LL(new)
10-Hydroxycamptothecin 17/	21	107124	NA, LE PS (268)	
Indicine N-Oxide 13/	3	132319	NA, PS (262), Bl, LE	LL, LL(new), KB
Isochondodendrine 11/	5	77035	KB	NA, PS
Isoharringtonine 14/	24	141634	LE, PS (209), KB	
Leurosine sulfate 6/	18	90636	LE, KB	
base		196522		
Liriodenine 7/	6	93621	KB	PS, SA
		215254		
Lunasine chloride 3/	22	80204	KB	LE, PS, NA, Bl, LL(new)
Lycorine 3,17/	14	401360	KB	SA, CA, LE, LL, NA
9-Methoxycamptothecin 4/	21	176323	Bl, LE, PS (217), LL(new)	
10-Methoxycamptothecin 17/	21	111533	LE	
5-Methoxycanthin-6-one 3/	15	58929	LL(new), KB	LE, PS, NA
Methoxydihydronitidine 17/	10	147789	PS (263), LE, KB	Bl, LL(new)
		146396		
9-Methoxyellipticine 3/	19	69187	PS (200), SA, LE, KB	NA
Methoxyharringtonine 17/	24	---	PS (214)	
N-Methyldemecolcine 11/	2	403150	KB	
O-Methylfagaronine 6/	10	166201	PS (200), LE	Bl, KB
4-Methylthiocanthin-6-one 3/	15	58928	KB	LE, NA
Monocrotaline 11/	3	28693	PS (133), NA, Bl, SA, CA	LL, LE, KB
Nitidine chloride 11,17/	10	146397	PS (260), LE, KB	Bl, LL(new)
Obamegin 1/	5	123123	KB	
Oxyacanthine 1,4/	5	93135	KB	LE, SA, NA
Oxynitidine 17/	10	135066	KB	PS

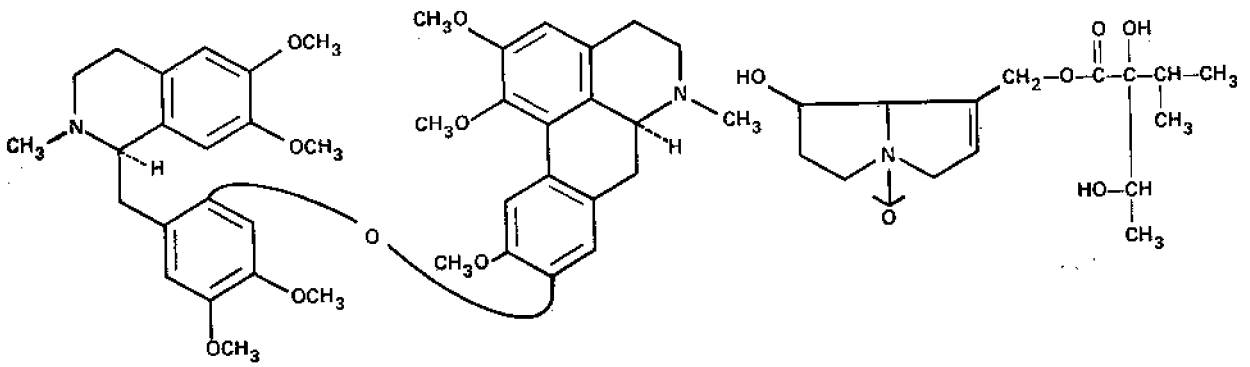
Table 20. - Alkaloids (continued)

	Class	NSC	Active	Inactive
Oxycylocerstrine 13/	13	65706	CA, LE, SA, PS (171), WA	
Pilocereine 17/	4	21075	KB	CA, LE, WA, SA, PS
Reserpine 3/	16	59272	SA, CA, WA	LE, BI, PS, KB
Sanguidimerine 6/	10	129231	KB	LE, PS, WA
Senecionine 11/	3	99935	WA, BI	LE, PS, KB
Senecionine N-oxide 11/	3	106677	WA	PS, LE, BI
β-Solamarine 11/	23	94735	SA, WA	
Solapalmatenine 11/	1	123125	WA, KB	LE
Solapalmatine 11/	1	123124	WA, KB	LE
Solaplumbin 4/	23	--	WA	
Solasodine hydrochloride 4/	23	35543	WA, LL	CA, LE, PS, SA, KB
Base		178260		
Base		179187		
Solasodine rhamnoside 4/	23	--	WA	
epi-Stephanine 11/	5	121392	WA	PS, KB
Stephavanine 11/	6	135026	LL	
Taxol 17/	20	125973	WA, LE, BI PS (190), KB	LL
α-Tetrasol 17/	20	--	KB	PS
Thalicarpine 11/	6	68075	LL, PS (130), WA, KB	LL, CA, LE LL(new), SA
Thalidasine 11/	5	90285	WA	KB
Tubulosine 17/	12	131547	LE, PS (186), KB	BI
Tylocrebrine 3,18/	13	60387	CA, LE PS (170), KB	BI, LL, LL(new SA, WA
Tylophorine 18/	13	76387	LE, SA	CA, WA
Tylophorinine 13/	13	100055	LE	
Voacamine 10,13/	18	82591	WA, SA	CA, LE, LL PS, BI, KB
Voacorine 13/	18	92072	WA	LE, SA

a/ Superscripts in this column refer to supplier numbers in table 3.

b/ The classes are numbered according to table 19.

ALKALOIDS

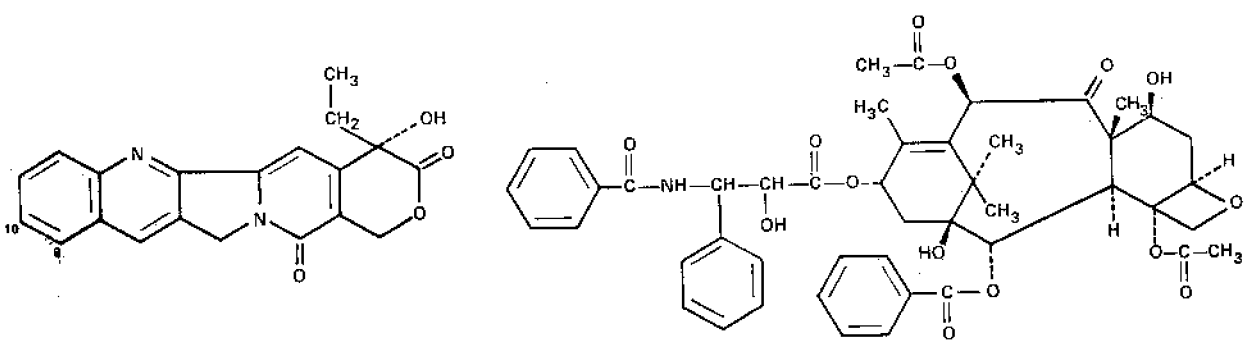


Thalicarpine
NSC-68075

Indicine N-oxide
NSC-132319

FIGURE 8

ALKALOIDS

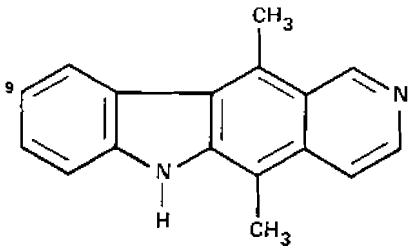


Camptothecin
NSC-94600

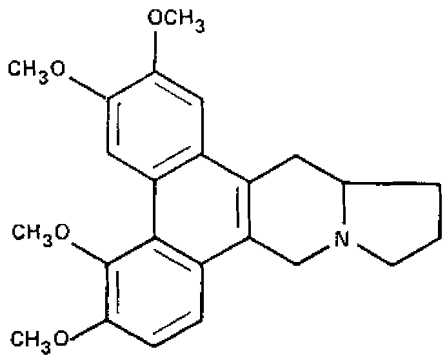
Taxol
NSC-125973

FIGURE 9

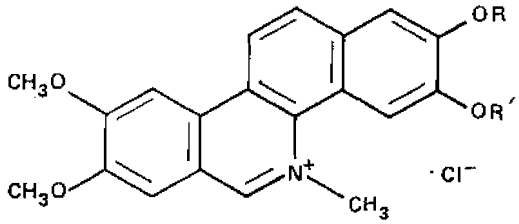
ALKALOIDS



Ellipticine
NSC-71795



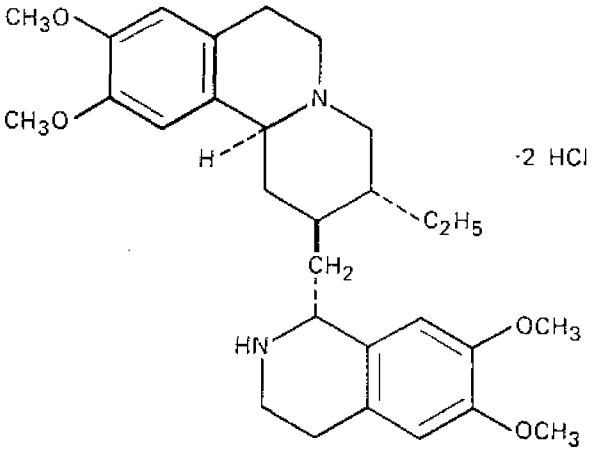
Tylocrebrine
NSC-60387



Nitidine chloride
NSC-146397 RR' = CH_2

Fagaronine
NSC-157995 R = H; R' = CH_3

FIGURE 10



Emetine hydrochloride

NSC-33669

FIGURE 11

(new) tumor. A simple addition reaction product of nitidine, methoxydihydronitidine, was obtained from the plant as an artifact (29) and showed similar activity. Advanced comparative screening is under way to determine which compound should be developed.

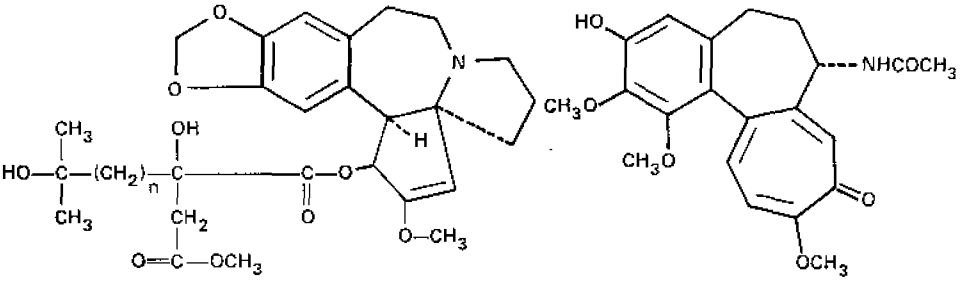
h. Emetine (fig 11).—This alkaloid, isolated in our program from *Cephaelis acuminata* Karst. (tables 3 and 20), but already an old commercial drug used as an amebicide, was given a clinical trial on the basis of its activity in P388 and L1210 leukemias. While there was some evidence of activity at high doses in lung carcinoma (≥ 50% reduction of tumor size in two cases) and in one case each of carcinoma of the trachea and of the thyroid gland (31), no response was demonstrated in several other malignancies (32).

i. Harringtonine and homoharringtonine (fig 12).—These alkaloids, together with isoharringtonine, isolated from *Cephalotaxus harringtonia* (Knight ex Forb.) R. Sm. var. *drupacea* (Sieb. & Zucc.) Koidz. (33), form a newly discovered type of active alkaloid which consists of complex esters of the inactive alcohol cephalotaxine. Lack of activity in the slow-growing tumors has lowered the priority on further development of these alkaloids, but the critical importance of the ester group for activity, a situation frequently encountered elsewhere, has stimulated efforts at synthesis designed to exploit the inherent activity of the esters; such efforts will hopefully provide compounds with broader activity.

j. 3-Desmethylcolchicine (fig 12).—This newly tested representative of an old class of active alkaloids was isolated from *Colchicum speciosum* Stev. (34). Certain advantages over other colchicine derivatives, one of which (demecolcine or V-deacetyl-V-methylcolchicine) has been declared (5) to be an established, clinically active antitumor agent, have revived interest in this group and sufficient quantities of this alkaloid are being obtained for further study.

Miscellaneous (table 21).—This table lists a small group of compounds that have antitumor activity but do not fall into one of the previous groups. None is particularly interesting except perhaps as an

ALKALOIDS



Harringtonine
NSC-124147 n = 2

Homoharringtonine
NSC-141633 n = 3

3-Desmethylcolchicine
NSC-172946

FIGURE 12

Table 21. - Miscellaneous

	NSC	Active	Inactive
Anacardic acid (?) 13/	106051	WA	
Anacardol (?) 13/	106050	WA	LE, LL, SA
Anemonin 17/	94101	KB	SA, LL, LE
			WA
Aristolochic acid 11/	11926 50413	CA, SA	PS, LE, LL KB
Shilgwanol (?) 13/	90250	WA	
Crotepoxide 11/	106396	LL, WA	PS, LE
5,7-Dihydroxy-8-methoxy-2-methylchromone 2/	251675	KB	
Dulcitol 6/	1944	PS (136)	CA, LE, SA
Gallic acid 12/	20103	KB	CA, LL, LE
			WA, PS, SA
Geiparvarin 19/	142227	PS (136), KB	BL, LE, LL
Gossypol 2/	56817	LL(new), WA	BL, CA, LE,
		PS (150)	SA, KB
Ipolearoside 4/	--	WA	
Jatropham 2/	177850	PS (125)	
Lignin 13/	115726	WA	LE, PS
Montanic acid monoglyceride 6/	--	PS (125)	PS
cis-1,8-Pentadecadiene 7/	138426	PS (127), WA	
1-Pentadecene 7/	77125	WA	LE, PS, SA
Rotenone 3,13,24/	8505 26258	PS (155), KB	CA, WA, LE LL, SA
Scopoletin 6/	405647	PS (133)	CA, LE, SA
			KB
T-Thujaplicin 2/	18805 43338 402794	KB	PS, WA, SA CA, LE, LL
d-Usnic acid 11/	5889	PS (135)	WA, BL, LE,
			LL, LL(new),
			KB
Uvaretin 2/	241906	PS (133), KB	BL

indicator of related compounds to acquire and test in the hope of finding improved activity. For readier reference, an alphabetical list (table 22) of all the compounds mentioned in the tables has been prepared.

COMMENTS AND CONCLUSIONS

The compounds which have been isolated from plants in the NCI program with activity against experimental tumors have been listed according to chemical type, along with the tumors against which they have shown activity and inactivity. Changes in methods of extraction and in the composition of the antitumor screen which have affected the identity and type of the compounds isolated are discussed.

It is evident that antitumor activity is encountered in compounds encompassing a wide variety of chemical classes. Many of these compounds are of novel chemical structure. On the basis of activity against experimental tumors thought to be most predictive of clinical effectiveness, it appears that certain chemical classes are of greater interest as a source of antitumor agents than others. Presently, the most interesting ones are the diterpenes, lignans, quassinoids, ansa macrolides, and alkaloids. Continued study of the plant kingdom will undoubtedly reveal other compounds in these classes that will be superior to existing ones, perhaps in possessing fewer toxic effects, and may also uncover other classes of compounds that will prove to be of high interest. In addition, it is expected that better plant sources of certain useful compounds will be found, as has been the case with maytansine.

A critical review of the antitumor properties of certain interesting compounds, as well as of some of the less interesting ones, will reveal fruitful areas for analog synthesis either from "scratch" or using existing compounds as templates. For example, a number of completely inactive alcohols have been converted into highly active esters simply by acylation.

Continued feedback of results from preclinical pharmacologic studies and from the clinic should result in modifications in the makeup of our bioassay screen and in the types of compounds that we are (and are not) seeking to test. Continued taxonomic analysis of plant sources of compounds should result in more selective collections for these compounds.

Table 22. – Cumulative index of compounds listed in these tables and their plants of origin (see table 23)

Compound entry no.	Name	NSC No.	Table No.	Plant entry no. (table 23)
C1	Acer saponin P	100045	14	P3
C2	Acer saponin Q	123429	14	P3
C3	2'-Acetylglaucarubinone	194251	16	P174, P175
C4	Acobioside A	116788	15	P7
C5	Acolongifloroside K	152149	15	P6
		173717		
C6	Acospectoside A	113569	15	P7
C7	Acovenoside A	116787	15	P6, P7
C8	Acovenoside B	116789	15	P7
C9	Adynerin	251673	15	P163
C10	Ailanthinone	238187k	16	P175
C11	Alkannin	94524	6	P28
C12	Alkannin β,β-dimethylacrylate	140377	6	P28
C13	Alkannin monoacetate	140376	6	P28
C14	Allamandicin	251691	7	P15
C15	Allamandin	251690	7	P15
--	Aloe-emodin	See Emodin	6	
C16	Ambrosin	85235	8	P127
C17	α-Amyrin	114787	11	P49, P184
C18	Anacardic acid (?)	106051	21	P19
C19	Anacardol (?)	106050	21	P19
C20	Anemonin	94101	21	P20, P21, P22
C21	Anopterine	179172	20	P24
C22	Apocannoside	83216	15	P25
C23	Arctiopicrine	177853	8	P63
C24	Aristolochic acid	11926	21	P27
		50413		
C25	Artemisiifolin	177852	8	P63
C26	Baileyin	179192	8	P36
C27	Berberine sulfate	5355	20	P26, P40, P76, P125, P210, P231
C28	Bersaldegenin 3-acetate	135076	15	P41
C29	Bersaldegenin 1,3,5-orthoacetate	135077	15	P41
C30	Bersamagenin 1,3,5-orthoacetate	135032	15	P41
C31	Berscillogenin	--	15	P41
C32	Bersenogenin	251692	15	P41
C33	Betulin	4644	11	P17, P18
C34	Betulinic acid	113090	11	P128, P189, P224
C35	Bodilawanol (?)	90250	21	P190a
C36	Bruceantarin	175399	16	P44, P45
C37	Bruceantin	165563	16	P44, P45
C38	Bruceantinol	238177	16	P44, P45
C39	Bruceine B	132793	16	P44, P45
--	Bufotalidin acetate	See Hellebrigenin 3-acetate	15	
C40	Burseran	123428	12	P47

Table 22. – Cumulative index of compounds listed in these tables and their plants of origin (see table 23) (continued)

Compound entry no.	Name	NSC No.	Table No.	Plant entry no. (table 23)
C41	Calotropin	143925	15	P32
		106393		
C42	Camptothecin	94600	20	P58, P152
C43	Celsioside C	173116	14	P63
C44	Centaureidin	106969	13	P35
C45	Cerberin	251674	15	P213
C46	Cesalin	110435	18	P53
C47	Chelidimerine	--	20	P69
C48	Corsulinine	251696	20	P73
C49	Colchicine	757	20	P74
C50	Colubrinol	196519	17	P75
C51	Colubrinol acetate	196520	17	P75
C52	Compound from Acanthospermum	--	8	P2
C53	" " Acer	--	14	P4
C54	" " Agave	--	14	P13
C55	" " "	137440	14	P13
C56	" " "	--	14	P13
C57	" " "	--	14	P13
C58	" " "	--	14	P11
C59	Compound from Agave	--	14	P12
C60	" " "	--	14	P10
C61	" " Alangium	92071	20	P14
C62	" " "	--	20	P14
C63	" " Allium	--	14	P16
C64	" " Asclepias	--	15	P31
C65	" " Aster	--	14	P33
C66	" " "	--	14	P34
C67	" " Bursera	--	11	P50
C68	" " Caesalpinia	--	18	P52
C69	" " Centaurea	--	8	P63
C70	" " Cevastium	--	18	P67
C71	" " Cercidium	--	18	P68
C72	" " Chrysopsis	--	14	P70
C73	" " Crossosoma	--	15	P80
C74	" " Cyclamen	135029	14	P86
C75	Compound from Dichroa	--	20	P91
C76	" " Elaeodendron	--	15	P96
C77	" " Entada	115727	14	P99
C77a	" " Gutierrezia	--	18	P115
C78	" " Hesperaloe	--	14	P122
C79	" " Ipomopsis	--	14	P131
C80	" " Jatropha	--	9	P134
C81	" " "	--	11	P134
C82	" " Machaeranthera	--	14	P149
C83	" " Maytenus	--	11	P156
C84	" " Mertensia	--	18	P158

Table 22. - Cumulative index of compounds listed in these tables and their plants of origin (see table 23) (continued)

Compound entry no.	Name	NSC No.	Table No.	Plant entry no. (table 23)
C85	" " Mirabilis	--	18	P159
C86	" " Muscari	--	18	P161
C87	" " Osteomeles	--	18	P167
C88	" " Rubia	--	11	P187
C89	" " Saponaria	77472	14	P188
C90	Compound from Solanum	--	14	P193
C91	" " Trillium	--	14	P216
C92	Compound B from Tylophora	85707	20	P218, P220
C93	" C " "	85708	20	P218, P220
C94	" D " "	85709	20	P218, P220
C95	" E " "	92070	20	P218
C96	" D " Tylophora indica	100056	20	P221
C97	" E " " "	100057	20	P221
C98	Conessine hydrochloride	32989	20	P124
C99	Coptisine chloride	119754	20	P69
C100	Coroglaucigenin	144150	15	P138
C101	Costunolide	106404	8	P142, P201
C102	Crinamine	88421	20	P79
C103	Crotepoxide	106396	21	P82
C104	Cryptopleurine	19912	20	P42
C105	Cryptowoline iodide	86342	20	P83
C106	Cucurbitacin D	49451	10	P39, P85, P89, P146, P153
C107	" D	521776	10	P39, P78, P84
C108	" D dehydroepirhamnoside	See Datiscocide	10	
C109	" E	106399	10	P71, P153
		521775		
C110	" F	--	10	P89
C111	" I	521777	10	P172
C112	" L	112167	10	P95
C113	" P	135074	10	P43
C114	" Q	135075	10	P43
C115	" glycoside	--	10	P89
C116	" "	--	10	P89
C117	" "	--	10	P89
C118	Cucurbitacin glycoside	--	10	P89
C119	Cycleadrine	--	20	P87
C120	Cycleanorine	--	20	P87
C121	Cycleapeltine	--	20	P87
C122	Cycloprocobuxine	102244	20	P51
C123	Cymarin	7522	15	P25, P168
C124	Damsin	85249	8	P110
C125	Datiscacin (Cucurbitacin R)	144154	10	P89
C126	Datiscoside (Cucurbitacin D dehydroepirhamnoside)	144153	10	P89
C127	Daucosterol (β-sitosterol glucoside)	165962	5	P177

Table 22. - Cumulative index of compounds listed in these tables and their plants of origin (see table 23) (continued)

Compound entry no.	Name	NSC No.	Table No.	Plant entry no. (table 23)
C128	Dehydroailanthinone	238188	16	P175
C129	Dehydroanhydropicropodophyllin	--	12	P46
C130	Dehydrobruceantarin	238178	16	P44
C131	Dehydrobruceantin	238178	16	P44, P45
C132	Dehydrobruceantol	238180	16	P44
C133	Demecolcine	3096	20	P74
		403147		
C134	3'-Demethylpodophyllotoxin	251681	12	P141
C135	Deoxypodophyllotoxin	403148	12	P46, P47, P48, P55, P121, P136, P141, P181, P214
C136	Desglucouzarin	--	15	P31
C137	5'-Desmethoxy-β-peltatin A methyl ether	126727	12	P46
C138	3-Desmethylcolchicine	172946	20	P74
C139	Desmethyltylophorinine	94739	20	P219, P221
C140	(-)-Dicentrine	--	20	P151
C141	Digitoxin	7529	15	P92
C142	Dihydrocucurbitacin B	106401	10	P39, P153
C143	5,7-Dihydroxy-8-methoxy-2-methylchromone	251675	21	P80
C144	(+)-Dimethylisolariciresinol-2α-xyloside	--	12	P41
C145	Dulcitol	1944	21	P156
C146	Elephantin	102817	8	P97
C147	Elephantopin	100046	8	P97
C148	Ellipticine	71795	20	P103, P105
C149	Emetine hydrochloride	33669	20	P64
C150	Emodin (aloe-emodin)	38628	6	P39, P185
C151	3-Epibersaccilogenin	135067	15	P41
C152	2-Epicucurbitacin B	See Isocucurbitacin B	10	
C153	10-Epieupatoroxin	135068	8	P102
C154	Epitulipinolide	142844	8	P142
C155	Erioflorin	144151	8	P100
C156	Erioflorin acetate	251667	8	P179
C157	Erioflorin methacrylate	251666	8	P179
C158	Eriolangin	182855	8	P100
C159	Eriolanin	144152	8	P100
C160	Eupachlorin	114567	8	P102
C161	Eupachlorin acetate	114568	8	P102
C162	Eupachloroxin	114570	8	P102
C163	Eupacunin	135020	8	P101
C164	Eupacunoxin	135021	8	P101
C165	Euparotin	104942	8	P102
C166	Euparotin acetate	104943	8	P102
C167	Eupatocunin	135025	8	P101

Table 22. - Cumulative index of compounds listed in these tables and their plants of origin (see table 23) (continued)

Compound entry no.	Name	NSC No.	Table No.	Plant entry no. (table 23)
C168	Eupatofolin	135023	8	P101
C169	Eupatoroxin	114569	8	P102
C170	Eupatundin	114566	8	P102
C171	Fagaronine	157995	20	P109
C172	Fastigilin B	176503	8	P36
C173	Fastigilin C	176507	8	P36
C174	N-Formyldesacetylcolchicine	403142	20	P74
C175	Gaillardin	106394	8	P111
C176	Gallic acid	20103	21	P166, P186
C177	Geiparvarin	142227	21	P111a
C178	Gitoxigenin	407807	15	P83
C179	Glaucarubinone	132791	16	P174, P175, P191
C180	Glaucarubolone	238189 126764	16	P175, P191
C181	Gnidicin	238941	9	P112
C182	Gnididin	238942	9	P112
C183	Gniditrin	238943	9	P112
C184	Gossypol	56817	21	P114, P160
C185	Harringtonine	124147	20	P65, P66
C186	Helenalin	85236	8	P38, P117, P118
C187	Helenalin acetate	166124	8	P29
C188	Hellebrigenin 3-acetate (Bufotalidin acetate)	106676	15	P41
C189	Hellebrigenin 3,5-diacetate	109330	15	P41
C190	Holacanthone	126763	16	P123
C191	Homoharringtonine	141633	20	P65
C192	16β-Hydroxybersaldegenin 1-acetate	135080	15	P41
C193	16β-Hydroxybersaldegenin 3-acetate	135079	15	P41
C194	16β-Hydroxybersaldegenin 1,3,5-orthoacetate	135078	15	P41
C195	16β-Hydroxybersamagenin 1,3,5-orthoacetate	251695	15	P41
C196	10-Hydroxycamptothecin	107124	20	P58
C197	12-Hydroxydaphnetoxin	239073	9	P88
C198	Hyrcanoside	--	15	P77
C199	Indicine N-Oxide	132319	20	P120
C200	Ipolearoside	--	21	P129
C201	Isobruceine B	238181	16	P44
C202	Isochondodendrine	77035	20	P87
C203	Isocucurbitacin B (2-Epicucurbitacin B)	106400	10	P153
C204	Isogaillardin	106395	8	P111
C205	Isoharringtonine	141634	20	P65
C206	Isoplumericine	112153	7	P15
C207	Jacaranone	251682	6	P132
C208	Jatropham	177850	21	P134

Table 22. - Cumulative index of compounds listed in these tables and their plants of origin (see table 23) (continued)

Compound entry no.	Name	NSC No.	Table No.	Plant entry no. (table 23)
C209	Jatrophone	135037	9	P132
C210	Justicidin B	254665	12	P172a
C211	Lapachol	11905	6	P198
C212	Leurosine base	196522	20	P60, P61
	Leurosine sulfate	90636	20	
C213	Liatrin	135034	8	P139
C214	Lignin	115726	21	P98
C215	Lipiferolide	251676	8	P142
C216	Liriodenine	93681	23	P23
		215254		
C217	Lunasine chloride	80204	20	P147, P148
C218	Lupeol	90487	11	P17, P18, P50, P208
C219	Lycorine	401360	20	P79, P126
C220	Maysenine	219974	17	P154
C221	Maysine	219972	17	P154
C222	Maytanacine	239387	17	P154, P183
C223	Maytanbutine	165014	17	P75, P116, P154, P155, P157, P183
C224	Maytanprine	165013	17	P116, P154, P155, P157, P182, P183
C225	Maytansine	153858	17	P116, P154, P155, P157, P182, P183
C226	Maytansinol	239386	17	P154
C227	Maytanvaline	219970	17	P116, P154
C228	9-Methoxycamptothecin	176323	20	P152
C229	10-Methoxycamptothecin	111533	20	P58
C230	5-Methoxycanthin-6-one	88929	20	P171
C231	Methoxydihydroaicidine	146396	20	P105, P106
		147789		
C232	9-Methoxyellipticine	69187	20	P103, P165
C233	Methoxyharringtonine	--	20	P66
C234	N-Methyldemecolcine	403150	20	P74
C235	O-Methylfagaronine	168201	20	P109
C236	4-Methylthiocanthin-6-one	88928	20	P171
C237	Mezerein	239072	9	P88
C238	Monocrotaline	28693	20	P81
C239	Montanic acid α-monoglyceride	--	21	P111b
C240	Myrsine saponin	123126	14	P162, P228
C241	Nardol diastereomer (?)	127084	8	P162a
C242	Neriifolin	123976	15	P211, P212, P213
C243	Nitidine chloride	146397	20	P104, P105, P106, P107, P108, P215, P231
C244	Normaysine	219973	17	P154
C245	Obamegin	123123	20	P229
C246	Oleandrigenin	148790	15	P83

Table 22. - Cumulative index of compounds listed in these tables and their plants of origin (see table 23) (continued)

Compound entry no.	Name	NSC No.	Table No.	Plant entry no. (table 23)
C247	Oleandrin	95089	15	P163
C248	Opposide	173716	15	P6
C249	Ovatifolin acetate	--	8	P179
C250	Oxyacanthine	93135	20	P40, P229
C251	Oxynitidine	135066	20	P106
C252	Oxytylocrebrine	85706	20	P218, P220
C253	Parthenolide	157035	8	P150
C254	Paucin	136722	8	P37
C255	α-Peltatin	24817	12	P30, P93
		35463		
C256	β-Peltatin	24819	12	P93
		35471		
C257	β-Peltatin A methyl ether	126726	12	P46
C258	cis-1,8-Pentadecadiene	138426	21	P95a
C259	1-Pentadecene	77125	21	P95a
C260	Pilocereine	21075	20	P144
C261	Plumericine	112152	7	P15
C262	Podolide	238978	9	P180
C263	Podophyllotoxin	24818	12	P135, P137, P141, P181
C264	Podophyllotoxin glucoside	163024	12	P56
C265	16-Propionylgitoxigenin	160843	15	P83
C266	Reserpine	59272	20	P103
C267	Rhodexin B	160843	15	P83
C268	Rotenone	8505	21	P90, P143, P176
		26258		
C269	Sanguidimerine	129231	20	P69
C270	Scilliglaucosidin	135036	15	P41, P222
C271	Scopoletin	405647	21	P119
C272	Senecionine	89935	20	P190
C273	Senecionine N-oxide	106677	20	P190
C274	β-Sitosterol	8096	5	P47, P57, P128, P130
		18173		P141, P145, P169
		49083		P170, P178, P184,
		86199		P208, P230
C275	β-Sitosterol glucoside	See Daucosterol	5	
C276	β-Solamarine	94735	20	P192
C277	Solapalmatenine	123125	20	P194
C278	Solapalmatine	123124	20	P194
C279	Solapiumbin	--	20	P164
C280	Solasodine base	178260	20	P164
		179187		
	Solasodine hydrochloride	35543	20	
C281	" rhamnoside	--	20	P164
C282	Somalin	251698	15	P8
C283	Steganacin	172958	12	P195
C284	Steganangin	172956	12	P195

Table 22. - Cumulative index of compounds listed in these tables and their plants of origin (see table 23) (continued)

Compound entry no.	Name	NSC No.	Table No.	Plant entry no. (table 23)
C285	Steganol	172959	12	P195
C286	Steganone	172957	12	P195
C288	epi-Stephanine	121392	20	P197
C289	Stephavanine	135026	20	P196
C290	Strophanthidin	86078	15	P168
C291	Taxifolin	36398	13	P94
C292	Taxodione	122419	6, 9	P202
C293	Taxodone	122420	6, 9	P202
C294	Taxol	125973	20	P203, P204, P205, P206, P207
C295	8 Tetraol	--	20	P204
C296	Thalicarpine	68075	20	P209
C297	Thalidasine	90285	20	P209
C298	β-Thujaplicin	18905 43338 402794	21	P1
C299	3',5,7-Trihydroxy-3,4'-dimethoxyflavone	106970	13	P35
C300	Tripdiolide	163063	9	P217
C301	Triptolide	163062	9	P217
C302	Triptonide	165677	9	P217
C303	Tubulosine	131547	20	P14
C304	Tulipinolide	106405	8	P142
C305	Tylocrebrine	60387	20	P218, P220
C306	Tylophorine	76387	20	P218, P220, P221
C307	Tylophorinine	100055	20	P218, P221
C308	Ursolic acid	4060	11	P9, P61, P163, P213, P224
C309	l-Usnic acid	5889	21	P72
C310	Uvaol	159627	11	P224
C311	Uvaretin	241906	21	P223
C312	Uzarigenin	119993	15	P113, P138
C313	Vernodalin	124459	8	P225
C314	Vernolepin	106398	8	P226
C315	Vernolide	124460	8	P225
C316	Vernomenin	116070	8	P226
C317	Vernomygdin	135072	8	P225
C318	Voacamine	82591	20	P199, P200, P227
C319	Voacorine	92072	20	P227
C320	Withacnistin	135073	15	P5
C321	Withaferin A	101088	15	P5, P173
C322	Zaluzanin C	177851	8	P230

Table 23. - Index of plants and active agents isolated therefrom

Plant entry no.	Name	Family	Compound entry no. (table 22)
P1	Abies concolor (Gord. & Glend.) Lindl. ex Hildebr.	Pinaceae	C298
P2	Acanthospermum glabratum (DC.) Wild	Asteraceae	C52
P3	Acer negundo L.	Aceraceae	C1, C2
P4	A. pensylvanicum L.	"	C53
P5	Dunalia arborescens (L.) Sleumer [Acnistus arborescens (L.) Schlecht.]	Solanaceae	C320, C321
P6	Acokanthera longiflora Stapf	Apocynaceae	C5, C7, C248
P7	A. oblongifolia (Hochst.) Codd	"	C4, C6, C7, C8
P8	Adenium obesum (Forskal) Roem. & Schult.	"	C282
P9	Adinandra dumosa Jack	Theaceae	C308
P10	Agave brandegeei Trel.	Agavaceae	C60
P11	A. caeciliana Berger	"	C58
P12	A. lechequilla Torr.	"	C59
P13	A. schottii Engelm.	"	C54, C55, C56, C57
P14	Alangium salvifolium (L.fil.) Wanger.	Alangiaceae	C61, C62, C303
P15	Allamanda cathartica L.	Apocynaceae	C14, C15, C206, C261
P16	Allium drummondii Regel	Liliaceae	C63
P17	Alnus firmifolia Fern.	Betulaceae	C33, C218
P18	A. rubra Bong [A. oregona Nutt.]	"	C33, C218
P19	Anacardium occidentale L.	Anacardiaceae	C18, C19
P20	Pulsatilla patens (L.) Mill. [Anemone patens L.]	Ranunculaceae	C20
P21	P. pratensis (L.) Mill. [Anemone pratensis L.]	"	C20
P22	P. vulgaris Mill. [Anemone pulsatilla L.]	"	C20
P23	Annona glabra L.	Annonaceae	C216
P24	Anopterus macleayanus F.Muell.	Saxifragaceae	C21
P25	Apocynum cannabinum L.	Apocynaceae	C22, C123
P26	Argemone mexicana L.	Papaveraceae	C27
P27	Aristolochia indica L.	Aristolochiaceae	C24
P28	Arnebia nobilis Rech.fil.	Boraginaceae	C11, C12, C13
P29	Arnica chamissonis Less. subsp. foliosa (Nutt.) Maguire var. incana (Gray) Hult.	Asteraceae	C287
P30	Asarum canadense L.	Aristolochiaceae	C255
P31	Asclepias albicans Wats.	Asclepiadaceae	C64, C136
P32	A. curassavica L.	"	C41
P33	Aster divaricatus L.	Asteraceae	C65
P34	A. glaucodes Blake	"	C66
P35	Baccharis sarothroides Gray	"	C44, C299
P36	Baileya multiradiata Harv. & Gray ex Torr.	"	C26, C172, C173
P37	B. pauciradiata Harv. & Gray ex Gray	"	C254
P38	Balduina angustifolia (Pursh) Robins.	"	C186
P39	Begonia X ruberhybrida Voss cv. "Alba"	Begoniaceae	C106, C107, C142
P40	Berberis asiatica Roxb. ex DC.	Berberidaceae	C27, C250
P41	Bersama abyssinica Fresen.	Melianthaceae	C28, C29, C30, C31, C32, C144, C151, C188, C189, C192, C193, C194, C195, C270

Table 23. - Index of plants and active agents isolated therefrom (continued)

Plant entry no.	Name	Family	Compound entry no. (table 22)
P42	Boehmeria cylindrica (L.) Sw.	Urticaceae	C104
P43	Brandegea bigelovii (Wats.) Cogn.	Cucurbitaceae	C113, C114
P44	Brucea antidysenterica J.F.Mill.	Simaroubaceae	C36, C37, C38, C39, C130, C131, C132, C201
P45	B. guineensis G.Don	"	C36, C37, C38, C39, C129, C131
P46	Bursera fagaroides (H.B.K.) Engl.	Burseraceae	C135, C137, C257
P47	B. microphylla Gray	"	C40, C135, C274
P48	B. morelensis Ramirez	"	C135
P49	B. schlechtendalii Engl.	"	C17
P50	B. simaruba (L.) Sarg.	"	C67, C218
P51	Buxus sempervirens L.	Buxaceae	C122
P53	Caesalpinia gilliesii (Hook.) D.Dietr.	Fabaceae	C46
P54	C. pulcherrima (L.) Sw.	"	C68
P55	Callitris columellaris F.Muell.	Cupressaceae	C135
P56	Callitris drumpondii (Parl.) F.Muell.	Cupressaceae	C264
P57	Calycogonium squamulosum Cogn.	Melastomataceae	C274
P58	Camptotheca acuminata Decne.	Nyssaceae	C42, C196, C229
P59	Cassia obtusa Clos	Fabaceae	C150
P60	Catharanthus lanceus (Boj. ex A.DC.) Pichon	Apocynaceae	C212
P61	C. pusillus (Murr.) C.Don	"	C212, C308
P62	Verbascum chinense (L.) Santapau [Celsia coromandeliana Vahl]	Scrophulariaceae	C43
P63	Centaurea melitensis L.	Asteraceae	C23, C25, C69
P64	Cephaelis acuminata Karst.	Rubiaceae	C149
P65	Cephalotaxus harringtonia (Knight ex Forb.) K.Sm. var. drupacea (Sieb. & Zucc.) Koidz.	Cephalotaxaceae	C185, C191, C205
P66	C. harringtonia cv. "Fastigiata"	"	C185, C233
P67	Cerastium texanum Britt.	Caryophyllaceae	C70
P68	Cercidium microphyllum (Torr.) Rose & Jtn.	Fabaceae	C71
P69	Chelidonium majus L.	Papaveraceae	C47, C99, C269
P70	Chrysopsis villosa (Pursh) Nutt. ex DC.	Asteraceae	C72
P71	Citrullus colocynthis (L.) Schrad.	Cucurbitaceae	C109
P72	Cladonia leptoclada desAbb.	Cladoniaceae	C309
P73	Cocculus pendulus (Forst.) Diels	Menispermaceae	C48
P74	Colchicum speciosum Stev.	Liliaceae	C49, C133, C138, C174, C234
P75	Colubrina texensis (Torr. & Gray) Gray	Rhamnaceae	C50, C51, C223
P76	Coptis teeta Wall.	Ranunculaceae	C27
P77	Coronilla varia L.	Fabaceae	C198
P78	Crinodendron bookerianum C.Gay	Elaeocarpaceae	C107
P79	Crinum macrantherum Engl.	Amaryllidaceae	C103, C219
P80	Crossosoma parviflorum Robins. & Fern.	Crossosomataceae	C73, C143
P81	Crotalaria spectabilis Roth	Fabaceae	C238
P82	Croton macrostachyus Hochst. ex Delile	Euphorbiaceae	C103
P83	Cryptocarya laevigata Bl. var. bowiei (Hook.) Kosterm. [C. bowiei (Hook.) Druce]	Lauraceae	C105

Table 23. - Index of plants and active agents isolated therefrom (continued)

Plant entry no.	Name	Family	Compound entry no. (table 22)
P84	Cryptostegia grandiflora R.Br.	Asclepiadaceae	C107, C178, C246, C265, C267
P85	Cucurbita digitata Gray	Cucurbitaceae	C106
P86	Cyclamen persicum Mill.	Primulaceae	C74
P87	Cyclea peltata (Lam.) Hook.fil. & Thoms.	Menispermaceae	C119, C120, C121, C202
P88	Daphne mezereum L.	Thymelaeaceae	C197, C237
P89	Datisca glomerata (Presl) Baill.	Datiscaceae	C106, C110, C115, C116, C117, C118, C119, C125, C126
P90	Derris trifoliata Lour.	Fabaceae	C268
P91	Dichroa febrifuga Lour.	Saxifragaceae	C75
P92	Digitalis purpurea L.	Scrophulariaceae	C141
P93	Diphylleia cymosa Michx.	Berberidaceae	C255, C256
P94	Drimys winteri Forst. & Forst.fil. var. chilensis (DC.) Gray	Winteraceae	C291
P95	Ecballium elaterium (L.) A.Rich	Cucurbitaceae	C112
P95a	Echinacea angustifolia DC.	Asteraceae	C258, C259
P96	Elaeodendron xylocarpum (Vent.) DC.	Celastraceae	C76
P97	Elephantopus elatus Bertol.	Asteraceae	C146, C147
P98	E. scaber L.	"	C214
P99	Entada phaseoloides (L.) Merr.	Fabaceae	C77
P100	Eriophyllum lanatum (Pursh) Forb.	Asteraceae	C155, C158, C159
P101	Eupatorium cuneifolium Willd.	"	C162, C163, C167, C168
P102	E. rotundifolium L.	"	C153, C160, C161, C162, C165, C166, C169, C170
P103	Bleekeria coccinea (Teysm. & Binnend.) Koidz. (Excavatia coccinea (Teysm. & Binnend.) Markgraf	Apocynaceae	C148, C232, C266
P104	Fagara chalybea (Engl.) Engl.	Rutaceae	C243
P105	F. leprieurii (Guillem., Perr. & A.Rich.) Engl.	"	C231, C243
P106	F. macrophylla (Oliv.) Engl.	"	C231, C243, C251
P107	Fagara rubrescens (Planch.) Engl.	Rutaceae	C243
P108	F. usambarensis Engl.	"	C243
P109	F. zanthoxyloides Lam.	"	C171, C235
P110	Ambrosia ambrosioides (Cav.) Payne [Franseria ambrosioides Cav.]	Asteraceae	C124
P111	Gaillardia pulchella Foug.	"	C175, C204
P111a	Geijera salicifolia Schott	Rutaceae	C177
P111b	Gnidia kraussiana Meissn.	Thymelaeaceae	C239
P112	G. lamprantha Gilg	"	C181, C182, C183
P113	Gomphocarpus physocarpus E.Meyer	Asclepiadaceae	C312
P114	Gossypium hirsutum L.	Malvaceae	C184
P115	Gutierrezia sarothrae (Pursh) Britt. & Rusby	Asteraceae	C77a
P116	Maytenus wightiana Babu [Gymnosporia rothiana (Wight & Arn.) Laws.]	Celastraceae	C223, C224, C225, C227
P117	Helenium autumnale L.	Asteraceae	C186
P118	H. microcephalum DC.	"	C186

Table 23. – Index of plants and active agents isolated therefrom (continued)

Plant entry no.	Name	Family	Compound entry no. (table 22)
P119	Melietta parvifolia (Gray ex Bemsl.) Benth.	Rutaceae	C271
P120	Heliotropium indicum L.	Boraginaceae	C199
P121	Hernandia ovigera L.	Hernandiaceae	C135
P122	Hesperaloe parviflora (Torr.) Coult.	Agavaceae	C78
P123	Holacantha emoryi Gray	Simaroubaceae	C190
P124	Holarrhena antidysenterica (L.) Wall. ex A.DC.	Apocynaceae	C98
P125	Hydrastis canadensis L.	Ranunculaceae	C27
P126	Hymenocallis latifolia (Mill.) M.J.Roem.	Amaryllidaceae	C219
P127	Hymenoclea salsola Torr. & Gray ex Gray	Asteraceae	C16
P128	Hyptis emoryi Torr.	Lamiaceae	C34, C274
P129	Ipomoea acuminata (Vahl) Roem. & Schult. [I. learii Paxt.]	Convolvulaceae	C200
P130	I. purpurea (L.) Roth	"	C274
P131	Ipomopsis aggregata (Pursh) V.Grant	Polemoniaceae	C79
P132	Jacaranda caucana Pittier	Bignoniaceae	C207
P133	Jatropha gossypiifolia L.	Euphorbiaceae	C209
P134	Jatropha macrorhiza Benth.	Euphorbiaceae	C80, C81, C208
P135	Juniperus chinensis L.	Cupressaceae	C263
P136	J. communis L. var. depressa Pursh	"	C135
P137	J. virginiana L.	"	C263
P138	Kanahia lanifolia (Forskal) R.Br.	Asclepiadaceae	C100, C312
P139	Liatris chapmanii Torr. & Gray	Asteraceae	C213
P140	Calocedrus decurrens (Torr.) Florin [Libocedrus decurrens Torr.]	Cupressaceae	C135
P141	Linum album Kotschy ex Boiss.	Linaceae	C134, C263, C274
P142	Liriodendron tulipifera L.	Magnoliaceae	C101, C154, C215, C304
P143	Lonchocarpus urucu Killip & A.C.Sm.	Fabaceae	C268
P144	Lophocereus schottii (Engelm.) Britt. & Rose	Cactaceae	C260
P145	Luffa echinata Roxb.	Cucurbitaceae	C274
P146	L. graveolens Roxb.	"	C106
P147	Lunasia amara Blanco	Rutaceae	C217
P148	Lunasia quercifolia (Warb.) K.Schum. & Lauterb.	Rutaceae	C217
P149	Machaeranthera linearis Greene	Asteraceae	C82
P150	Magnolia grandiflora L.	Magnoliaceae	C253
P151	M. virginiana L.	"	C140
P152	Mappia foetida (Wight) Miers	Icacinaceae	C42, C228
P153	Marah oreganus (Torr. & Gray) T.J.Howell	Cucurbitaceae	C106, C109, C142, C203
P154	Maytenus buchananii (Loes.) R.Wilczek	Celastraceae	C220, C221, C222, C223, C224, C225, C226, C227
P155	M. heterophylla (Eckl. & Zeyh.) N.Robson	"	C223, C224, C225
P156	M. senegalensis (Lam.) Exell	"	C83, C143
P157	M. serrata (Hochst. ex A.Rich.) R.Wilczek	"	C223, C224, C225
P158	Mertensia franciscana Heller	Boraginaceae	C84
P159	Mirabilis multiflora (Torr.) Gray	Nyctaginaceae	C85
P160	Montezuma speciosissima Sesse & Moc.	Malvaceae	C184

Table 23. - Index of plants and active agents isolaced therefrom (continued)

Plant entry no.	Name	Family	Compound entry no. (table 22)
P161	Muscari comosum Mill.	Liliaceae	C86
P162	Myrsine africana L.	Myrsinaceae	C240
P162a	Nardostachys jatamansi DC.	Valerianaceae	C241
P163	Nerium oleander L.	Apocynaceae	C9, C247, C308
P164	Nicotiana plumbaginifolia Viv.	Solanaceae	C279, C280, C281
P165	Ochrosia moorei (F.Muell.) F.Muell.	Apocynaceae	C148, C232
P166	Oenothera caespitosa Nutt.	Onagraceae	C176
P167	Osteomeles schwerinae Schneid.	Rosaceae	C87
P168	Parquetina nigrescens (Afzel.) Bullock	Asclepiadaceae	C123, C290
P169	Parthenocissus inserta (A.J.Kern.) Fritsch	Vitaceae	C274
P170	Penstemon deustus Dougl. ex Lindl.	Scrophulariaceae	C274
P171	Pentaceras australis (F.Muell.) Hook.fil ex Benth.	Rutaceae	C230, C236
P172	Phormium tenax Forst. & Forst.fil	Agavaceae	C111
P172a	Phyllanthus brasiliensis (Aubl.) Poir.	Euphorbiaceae	C210
P173	Physalis virginiana Mill. var. sonorae (Torr.) Waterfall [P. longifolia Nutt.]	Solanaceae	C321
P174	Picrasma excelsa (Sw.) Planch.	Simaroubaceae	C3, C179
P175	Pierreodendron kerstingii (Engl.) Little	"	C3, C10, C128, C179, C180
P176	Piscidia erythrina (L.) Sarg.	Fabaceae	C268
P177	Pleocarpnus revolutus D.Don	Asteraceae	C127
P178	Plumeria acutifolia Poir.	Apocynaceae	C274
P179	Podanthus ovatifolius Lag.	Asteraceae	C156, C157, C249
P180	Podocarpus gracilior Pilg.	Podocarpaceae	C262
P181	Podophyllum pleianthum Hance	Berberidaceae	C135, C263
P182	Putterlickia pyracantha (L.) Endl.	Celastraceae	C224, C225
P183	P. verrucosa (E.Meyer ex Sonder) Szyszy.	"	C222, C223, C224, C225
P184	Pyrus pashia Buch.-Ham. ex D.Don	Rosaceae	C17, C274
P185	Rhamnus frangula L.	Rhamnaceae	C150
P186	Rhus trilobata Nutt.	Anacardiaceae	C176
P187	Rubia tenuifolia Urv.	Rubiaceae	C29
P188	Saponaria officinalis L.	Caryophyllaceae	C39
P189	Sarracenia flava L.	Sarraceniaceae	C34
P190	Senecio triangularis Hook.	Asteraceae	C272, C273
P190a	Semecarpus anacardium L.fil.	Anacardiaceae	C35
P191	Simarouba glauca DC.	Simaroubaceae	C179, C180
P192	Solanum dulcamara L.	Solanaceae	C276
P193	S. marginatum L.fil.	"	C90
P194	S. tripartitum Dun.	"	C277, C278
P195	Steganotaenia araliacea Hochst.	Apiaceae	C283, C284, C285, C286
P196	Stephania abyssinica (Dillon & A.Rich.) Walp.	Menispermaceae	C289
P197	S. japonica (Thunb. ex Murr.) Miers var. discolor (Blume) Forman [S. hernandiifolia (Willd.) Walp.]	"	C288
P198	Stereospermum suaveolens (Roxb.) DC.	Bignoniaceae	C211

Table 23. - Index of plants and active agents isolated therefrom (continued)

Plant entry no.	Name	Family	Compound entry No. (table 22)
P199	Tabernaemontana johnstonii (Stapf) Pichon	Apocynaceae	C318
P200	T. ventricosa Hochst. ex A.DC. [T. usambarensis K.Schum ex Engl.]	"	C318
P201	Talauma ovata St.-Hil.	Magnoliaceae	C101
P202	Taxodium distichum (L.) M.Rich.	Taxodiaceae	C292, C293
P203	Taxus baccata L. cv. "Fastigiata"	Taxaceae	C294
P204	T. brevifolia Nutt.	"	C294, C295
P205	T. canadensis Marsh.	"	C294
P206	T. cuspidata Sieb. & Zucc.	"	C294
P207	T. X media Rehd.	"	C294
P208	Teclea verdoorniana Exell & Mendonca [T. grandifolia Engl.]	Rutaceae	C218, C274
P209	Thalictrum dasycarpum Fisch., Mey. & Ave-Lall.	Ranunculaceae	C296, C297
P210	T. flavum L. subsp. glaucum (Desf.) Batt. [T. rugosum Ait.]	"	C27
P211	Thevetia ahouai (L.) A.DC.	Apocynaceae	C242
P212	T. ovata (Cav.) A.DC.	"	C242
P213	T. peruviana (Pers.) K.Schum.	"	345, C242, C308
P214	Thuja occidentalis L.	Cupressaceae	C125
P215	Toddalia asiatica (L.) Lam.	Rutaceae	C243
P216	Trillium erectum L.	Liliaceae	C91
P217	Tripterygium wilfordii Hook.fil.	Celastraceae	C300, C301, C302
P218	Tylophora crebriflora S.T.Blake	Asclepiadaceae	C92, C93, C94, C95, C252, C305, C306, C307
P219	T. dalzellii Hook.fil.	"	C139
P220	T. hirsuta (Wall.) Wight	"	C92, C93, C94, C252, C305, C306
P221	T. indica (Burm.fil.) Merr.	"	C96, C97, C139, C306, C307
P222	Urginea altissima (L.fil.) Baker	Liliaceae	C270
P223	Uvaria acuminata Oliv.	Annonaceae	C311
P224	Vauquelinia corymbosa Correa ex Humb. & Bonpl.	Rosaceae	C34, C308, C310
P225	Vernonia amygdalina Delile	Asteraceae	C313, C315, C317
P226	V. hymenolepis A.Rich.	"	C314, C316
P227	Voacanga africana Stapf ex G.Bell.	Apocynaceae	C318, C319
P228	Wallenia yunquensis (Urban) Mez	Myrsinaceae	C240
P229	Xanthorrhiza simplicissima Marsh.	Ranunculaceae	C245, C250
P230	Zaluzania parthenioides (DC.) Rzed. [Z. robinsonii Sharp]	Asteraceae	C274, C322
P231	Zanthoxylum monophyllum (Lam.) P.Wils.	Rutaceae	C27, C243

Table 24. - Plant families and genera from Table 23

ACERACEAE
- Acer

AGAVACEAE
- Agave
- Hesperaloe
- Phormium

ALANGIACEAE
- Alangium

AMARYLLIDACEAE
- Crinum
- Hymenocallis

ANACARDIACEAE
- Anacardium
- Rhus
- Semecarpus

ANNONACEAE
- Annona
- Uvaria

APIACEAE
- Steganotaenia

APOCYNACEAE
- Acokanthera
- Adenium
- Allamanda

APOCYNACEAE
- Apocynum
- Bleekeria
- Catharanthus
- Holarrhena
- Nerium
- Ochrosia
- Plumeria
- Tabernaemontana
- Thevetia
- Voacanga

ARISTOLOCHIACEAE
- Aristolochia
- Asarum

ASCLEPIADACEAE
- Asclepias
- Cryptostegia
- Gomphocarpus
- Kanahia
- Parquetina
- Tylophora

ASTERACEAE
- Acanthospermum
- Ambrosia
- Arnica
- Aster
- Baccharis
- Baileya
- Balduina
- Centaurea
- Chrysopsis
- Echinacea
- Elephantopus
- Eriophyllum
- Eupatorium
- Gaillardia
- Gutierrezia
- Helenium
- Hymenoclea
- Liatris
- Machaeranthera
- Pleocarpus
- Podanthus
- Senecio
- Vernonia
- Zaluzania

BEGONIACEAE
- Begonia

BERBERIDACEAE
- Berberis
- Diphylleia
- Podophyllum

BETULACEAE
- Alnus

BIGNONIACEAE
- Jacaranda
- Stereospermum

BORAGINACEAE
- Arnebia
- Heliotropium
- Mertensia

BURSERACEAE
- Bursera

BUXACEAE
- Buxus

CACTACEAE
- Lophocereus

CARYOPHYLLACEAE
- Cerastium
- Saponaria

CELASTRACEAE
- Elaeodendron
- Maytenus
- Putterlickia
- Tripterygium

CEPHALOTAXACEAE
- Cephalotaxus

CLADONIACEAE
- Cladonia

COMPOSITAE
- See Asteraceae

CONVOLVULACEAE
- Ipomoea

CROSSOSOMATACEAE
- Crossosoma

CUCURBITACEAE
- Brandegea
- Citrullus
- Cucurbita
- Echallium
- Luffa
- Marah

CUPRESSACEAE
- Callitris
- Calocedrus
- Juniperus
- Thuja

DATISCACEAE
- Datisca

ELAEOCARPACEAE
- Crinodendron

EUPHORBIACEAE
- Croton
- Jatropha
- Phyllanthus

FABACEAE
- Caesalpinia
- Cassia
- Cercidium
- Coronilla
- Crotalaria
- Derris
- Entada
- Lonchocarpus
- Piscidia

HERNANDIACEAE
- Hernandia

ICACINACEAE
- Mappia

LABIATAE
- See Lamiaceae

LAMIACEAE
- Hyptis

LAURACEAE
- Cryptocarya

LEGUMINOSAE
- See Fabaceae

LILIACEAE
- Allium
- Colchicum
- Muscari
- Trillium
- Urginea

LINACEAE
- Linum

MAGNOLIACEAE
- Liriodendron
- Magnolia
- Talauma

MALVACEAE
- Gossypium
- Montezuma

MELASTOMATACEAE
- Calycogonium

MELIANTHACEAE
- Bersama

MENISPERMACEAE
- Cocculus
- Cyclea
- Stephania

MYRSINACEAE
- Myrsine
- Wallenia

NYCTAGINACEAE
- Mirabilis

NYSSACEAE
- Camptotheca

ONAGRACEAE
- Oenothera

PAPAVERACEAE
- Argemone
- Chelidonium

PINACEAE
- Abies

PODOCARPACEAE
- Podocarpus

POLEMONIACEAE
- Ipomopsis

PRIMULACEAE
- Cyclamen

RANUNCULACEAE
- Coptis
- Hydrastis
- Pulsatilla
- Thalictrum
- Xanthorrhiza

RHAMNACEAE
- Colubrina
- Rhamnus

ROSACEAE
- Osteomeles
- Pyrus
- Vauquelinia

RUBIACEAE
- Cephaelis
- Rubia

RUTACEAE
- Fagara
- Galipea
- Galietta
- Lunasia
- Pentaceras
- Teclea
- Toddalia
- Xanthoxylum

SARRACENIACEAE
- Sarracenia

SAXIFRAGACEAE
- Astilbe
- Dichroa

SCROPHULARIACEAE
- Digitalis
- Penstemon
- Verbascum

SIMAROUBACEAE
- Brucea
- Holacantha
- Picrasma
- Picrreodendron
- Simaruba

SOLANACEAE
- Datura
- Nicotiana
- Physalis
- Solanum

TAXACEAE
- Taxus

TAXODIACEAE
- Taxodium

THEACEAE
- Adinandra

THYMELAEACEAE
- Daphne
- Gnidia

UMBELLIFERAE
- See Apiaceae

URTICACEAE
- Boehmeria

VALERIANACEAE
- Nardostachys

VITACEAE
- Parthenocissus

ZINNIRACEAE
- Drimys

REFERENCES

1. HARTWELL JL. Plants used against cancer. A survey. Lloydia 30:379–436, 1967, and ten additional installments ending with 34:386–437, 1971.
2. HARTWELL JL, and SCHRECKER AW. The chemistry of podophyllum. *In* Progress in the Chemistry of Organic Natural Products (Zechmeister L, ed). Vienna, Springer Verlag, 1958, vol 15, pp 83–166.
3. MAINE WRITERS RESEARCH CLUB. Maine Indians in History and Legends. Portland, Me, Severn-Wylie-Jewett Co, 1952, pp 96–102.
4. KOST J. The Elements of Materia Medica and Therapeutics. Cincinnati, Kost and Pool, 1849, 572 pp.
5. GOLDIN A, SERPICK AA, and MANTEL N. A commentary. Experimental screening procedures and clinical predictability value. Cancer Chemother Rep 50:173–218, 1966.
6. HARTWELL JL, and ABBOTT BJ. Antineoplastic principles in plants: recent developments in the field. *In* Advances in Pharmacology and Chemotherapy (Garattini S, Goldin A, Hawking F, et al, eds). New York, Academic Press, Inc, 1969, vol 7, pp 117–209 (*see* pp 154 and 194).
7. WALL ME, TAYLOR H, AMBROSIO L, ET AL. Plant antitumor agents. III. A convenient separation of tannins from other plant constituents. J Pharm Sci 58:839–841, 1969.
8. BLOCK JB, SERPICK AA, MILLER W, ET AL. Early clinical studies with lapachol (NSC-11905). Cancer Chemother Rep Part 2, vol 4(4):27–28, 1974.
9. KUPCHAN SM, DESSERTINE AL, BLAYLOCK BT, ET AL. Isolation and structural elucidation of allamandin, an antileukemic iridoid lactone from *Allamanda cathartica*. J Org Chem 39: 2477–2482, 1974.
10. KUPCHAN SM, AYNEHCHI Y, CASSADY JM, ET AL. The isolation and structural elucidation of two novel sesquiterpenoid tumor inhibitors from *Elephantopus elatus*. J Am Chem Soc 88:3674–3676, 1966.
11. KUPCHAN SM, COURT WA, DAILEY RG, JR, ET AL. Triptolide and tripdiolide. Novel antileukemic diterpenoid triepoxides from *Tripterygium wilfordii*. J Am Chem Soc 94:7194–7195, 1972.
12. DOSKOTCH RW, MALIK MY, and BEAL JL. Cucurbitacin B, the cytotoxic principle of *Begonia tuberhybrida* var. *alba*. Lloydia 32:115–122, 1969.
13. NISSEN NI, LARSEN V, PEDERSEN H, ET AL. Phase I clinical trial of a new antitumor agent, 4′-demethylepipodophyllotoxin 9-(4,6-*O*-ethylidene-β-D-glucopyranoside) (NSC-141540; VP-16-213). Cancer Chemother Rep 56:769–777, 1972.
14. KUPCHAN SM, TAKASUGI M, SMITH RM, ET AL. Tumor inhibitors. LXII. The structures of acerotin and acerocin, novel tripterpene ester aglycones from the tumor inhibitory saponins of *Acer negundo*. J Org Chem 36:1972–1976, 1971.
15. KUPCHAN SM, BRITTON RW, ZIEGLER MF, ET AL. Bruceantin, a new potent antileukemic simaroubolide from *Brucea antidysenterica*. J Org Chem 38:178–179, 1973.
16. WALL ME, and WANI M. The isolation and structure of holacanthone, a potent experimental antitumor agent. (Abstr) *In* Proceedings of the 7th International Symposium on Chemical Natural Products, Riga, USSR, 1970, E138, p 72.
17. KUPCHAN SM, KOMODA Y, COURT WA, ET AL. Maytansine, a novel antileukemic ansa macrolide from *Maytenus ovatus*. J Am Chem Soc 95:1354–1356, 1972.
18. WANI MC, TAYLOR HL, and WALL ME. Plant antitumor agents: colubrinol acetate and colubrinol, antileukaemic ansa macrolides from *Colubrina texensis*. J Chem Soc Chem Commun 470:390, 1973.
19. ULUBELEN A, MCCAUGHEY WF, and COLE JR. Proteinaceous antitumor substances from plants. III. *Caesalpinia gilliesii* (Leguminosae). J Pharm Sci 56:914–916, 1967.
20. KUPCHAN SM, and YOKOYAMA N. The structure, configuration and synthesis of thalicarpine, a novel dimeric aporphine-benzylisoquinoline alkaloid. J Am Chem Soc 85:1361–1362, 1963.
21. WALL ME, WANI MC, COOK CE, ET AL. Plant antitumor agents. I. The isolation and structure of camptothecin, a novel alkaloidal leukemia and tumor inhibitor from *Camptotheca acuminata*. J Am Chem Soc 88:3888–3890, 1966.
22. GOTTLIEB JA, GUARINO AM, CALL JB, ET AL. Preliminary pharmacologic and clinical evaluation of camptothecin sodium (NSC-100880). Cancer Chemother Rep 54:461–470, 1970.
23. WANI MC, and WALL ME. Plant antitumor agents. II. The structure of two new alkaloids from *Camptotheca acuminata*. J Org Chem 34:1364–1367, 1969.
24. GOVINDACHARI TR, and VISWANATHAN N. 9-Methoxycamptothecin. A new alkaloid from *Mappia foetida* Miers. Indian J Chem 10:453–454, 1972.
25. WANI MC, TAYLOR HL, WALL ME, ET AL. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. J Am Chem Soc 93:2325–2327, 1971.
26. LODER JW. The structure of methoxyellipticine. Aust J Chem 19:1947–1950, 1966.
27. MATHE G, HAYAT M, DE VASSAL F, ET AL. Methoxy-9-ellipticine lactate. III. Clinical screening: its action in acute myeloblastic leukaemia. Rev Eur Etud Clin Biol 15:541–545, 1970.
28. GELLERT E, GOVINDACHARI TR, LAKSHMIKANTHAM MV, ET AL. The alkaloids of *Tylophora crebriflora*; structure and synthesis of tylocrebrine, a new phenanthroindolizidine alkaloid. J Chem Soc, pp 1008–1014, 1962.
29. WALL ME, WANI MC, and TAYLOR HL. Plant anti-tumor agents. VIII. Isolation and Structure of Anti-tumor Alkaloids from *Fagara macrophylla*. (Abstr) *In* Proceedings of the 162nd National Meeting of the American Chemical Society, Washington, DC, Sept 12–17, 1971. MEDI 34.
30. MESSMER WM, TIN-WA M, FONG HHS, ET AL. Fagaronine, a new tumor inhibitor isolated from *Fagara zanthoxyloides* Lam. (Rutaceae). J Pharm Sci 61:1858, 1972.
31. PANETTIERE F, and COLTMAN CA, JR. Phase I experience with emetine hydrochloride (NSC-33669) as an antitumor agent. Cancer 27:835–841, 1971.
32. SIDDIQUI S, FIRAT D, and OLSHIN S. Phase II study of emetine (NSC-33669) in the treatment of solid tumors. Cancer Chemother Rep 57:423–428, 1973.
33. POWELL RG, WEISLEDER D, SMITH CR, JR, ET AL. Structure of cephalotaxine and related alkaloids. Tetrahedron Lett 46:4081–4084, 1969.
34. KUPCHAN SM, BRITTEN RN, CHIANG CK, ET AL. Tumor inhibitors. 88. The antileukemic principles of *Colchicum speciosum*. Lloydia 36:338–340, 1973.