New Natural Products Under Development at the National Cancer Institute

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Summary

Twenty-six new agents of natural products origin which are under preclinical development as potential antitumor agents at the National Cancer Institute are discussed with reference to their sources, structures, antitumor activity, current status, and future potential as clinically effective drugs.

Introduction

Since 1956 the Cancer Chemotherapy National Service Center, now incorporated into the Developmental Therapeutics Program (DTP), Division of Cancer Treatment, has had a comprehensive drug development program that includes the screening of compounds obtained from natural products [7]. Since the inception of the program, approximately 178,802 microbial cultures have been isolated and fermented and 103,272 plants extracted. The fermentation broths and plant extracts have been tested for their cell cytotoxicity and in vivo activity against various animal tumors using standard protocols [10]. During the last 3 years the fermentation broths in many cases have first been tested in various in vitro prescreens (e.g., enzyme inhibition, tubulin binding, phage induction, antimicrobial and antiyeast screens) [6]. Approximately 7 years ago a concentrated effort to evaluate animal products (primarily marine) was initiated and to date 13,751 extracts have been screened and 0.7% showed confirmed in vivo activity.

Many compounds have been isolated from the above-mentioned programs and in addition many natural products are obtained from the NCI worldwide surveillance program which includes agreements with industrial companies, research institutes, universities, and scientists. Some of the more interesting compounds in preclinical drug development that will be discussed are listed in Table 1. Many of the compounds discussed are analogs of earlier compounds which have been prepared in an effort to discover second generation drugs which retain the activity of the parent molecule and have less toxicity.

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Table 1. Natural products undergoing preclinical drug development at NCI

Compound	NCI No.
Actinomycin pip 1β	107660
Azetomycin 1	244392
Actinomycin S_3	296940
Pepleomycin	276382
Bleomycin BAPP	294979
Tallysomycin A	279496
Aclacinomycin A	208734
7-0-methyl nogarol	269148
Nogamycin	265450
Echinomycin	526417
Valinomycin	122023
Largomycin	237020
Aphidicolin	234714
Neothramycin	285223
Rapamycin	226080
CC-1065	298223
Borrelidin	216128
Eriofertopin	283439
Homoharringtonine	141633
Tripdiolide	163063
Taxol	125973
Baccharin	269757
Isobaccharin	269760
Phyllanthoside	266492
Fagaronine	157995
Psorospermin	266491

Methodology

Natural products, when purified ($> 90\%$), are assigned NSC numbers which are identification codes used by NCI for all compounds studied. NCI prefers materials to be at least 98% pure before assigning NCS numbers; however, because proteins, peptides, polysaccharides, and some other antibiotics do not lend themselves to easy purification or are extremely costly to purify to a state of $> 90\%$ purity, they are assigned NSC numbers also. The various protocols for screening these drugs have been established by the Drug Evaluation Branch, NCI [10]. Normally the P388 leukemia assay in mice is the first in vivo test in which a natural product compound is evaluated. However, rational selection can result in using another in vivo tumor as the first screen if there is information on organ distribution, lipophilicity, selective tissue effects, or other antitumor data that indicate that other testing is preferable.

In most cases a material is tested initially against the P388 leukemia (PS) to determine toxicity data even though this may not be the test tumor of greatest interest. If reproducible activity is demonstrated in PS as evidenced by an increase in life span (ILS) of 20% or greater and if the compound has a novel structure, it is tested against a panel of tumors (Table 2). Close analogs of known compounds are tested under special

Table 2. Division of Cancer Treatment (DCT) panel of antiserum screens

Tumor	Parameter	Activity criteria	Route inocula-tion	Tissue and level of inoculation	
Mouse colon 38 (C8)	Tumor inhibition	T/C ≤ 42%	IP	Brei	1 : 100
Mouse Breast (CD)	Tumor inhibition	T/C ≤ 42%	SC	Brei	5×10^6
Human colon xenograft	Tumor inhibition	T/C ≤ 42%	SC	Fragment	14 mg
Mouse breast xenograft	Tumor inhibition	T/C ≤ 42%	SC	Fragment	14 mg
Mouse lung xenograft	Tumor inhibition	T/C ≤ 42%	SC	Fragment	14 mg
Mouse B16 melanosarcoma (B 16)	Survival	T/C ≥ 125%	IP	Brei	1 : 10
Mouse Lewis lung carcinoma (LL)	Survival	T/C ≥ 140%	IP	Cells	10^5
Mouse L1210 leukemia (LE)	Survival	T/C ≥ 125%	IP	Cells	10^5

protocols in comparison with the parent compound. Rational bypass can be used to expedite testing in tumor panel systems or to screen against tumors that are not part of the tumor panel, including, for example, brain tumors for compounds that are known to cross the blood brain barrier or hormone dependent tumors for compounds with endocrine activity.

If the compound has sufficient activity and is a novel structure or an analog deemed of interest to NCI, it will now be reviewed by the Decision Network (DN) Committee and, if approved, is scheduled for formulation studies. When a clinical formulation is obtained, the agent is tested for schedule dependency and oral route activity. The DN group then determines if the compound should progress into toxicology studies. While toxicology studies are being done, the pharmacology group determines pharmacokinetics and tissue distribution of this drug. The DN Committee reviews the toxicology results and determines if the drug is suitable for Phase I clinical trials. After Phase I trials are completed, the DN group again reviews the results and determines if the drug should be a candidate for Phase II clinical trials against the panel of human tumors selected by NCI:

1. Breast
2. Colon
3. Lung
4. Melanoma
5. Acute leukemia
6. Lymphoma, Hodgkin's disease

Natural products, whether derived from microbes, plants, or animals, are all evaluated in the same way. Thorough discussions of the methodologies used in development of fermentation-derived compounds and plant-derived compounds are found in the paper by Douros [6] and Suffness and Douros [26].

Results

The following drugs derived from natural sources are now in some phase of preclinical drug development at NCI:

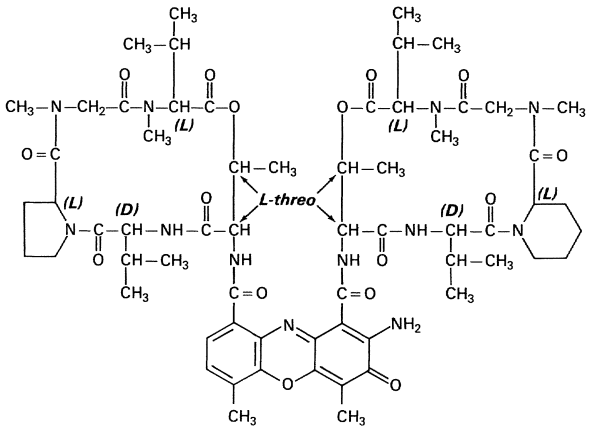

Fig. 1. Structure of actinomycin pip 1β (NSC 107660)

Actinomycin pip 1β (NSC-107660) (Fig. 1) is a peptide antibiotic with a phenoxazine chromophore that is produced by *Streptomyces parvulus*. This antibiotic differs from actinomycin D in that the proline residue in the *beta* peptide chain is replaced with pipecolic acid. The production of actinomycin pip 1β and actinomycins in general by precursor feeding has been extensively studied by Katz and co-workers [8, 12]. There is interest in evaluation of a new actinomycin in clinical trial if the compound gives indication of a broader or different spectrum of activity, less toxicity, or a better chemotherapeutic index than actinomycin D. More than 100 actinomycins have been evaluated in NCI's program and three seem to have activities of interest. Actinomycin pip 1β is being compared with actinomycin D in gastrointestinal toxicity tests and in the NCI tumor panel. Actinomycin pip 1β has shown good activity in murine tumors against colon 38 (C8) giving 91% inhibition, mammary carcinoma (CD) 99% inhibition, colon 26 (C6) 84% increased life span (ILS), B16 melanoma 66% ILS, L1210 leukemia (LE) 59% ILS, P388 leukemia (PS) 105% ILS. These activities are quite similar to those of actinomycin D. The critical data will be whether gastrointestinal toxicity is considerably less than that of actinomycin D and whether some xenograft activity is found with this analog. If actinomycin pip 1β is superior to actinomycin D in these tests it will be presented to DN. A comparison of the various actinomycin activities can be found in Table 3.

Azetomycin I (NSC-244392) (Fig. 2) is an analog of actinomycin D and is also obtained by precursor fermentation [8]. This antibiotic differs from actinomycin D in that one of the prolines is replaced with azetidine. This compound has shown good activity against P388 giving 166% ILS, 51% ILS against LE, 52% against B16, 100% inhibition of CD, 57% ILS against C6 (Table 3). This drug has also shown activity against an actinomycin D-resistant leukemia. One additional actinomycin is being tested, actinomycin S_3 (NSC-296940) [9]. The spectrum of antitumor activity in the few tests evaluated is inferior to that of actinomycin D (Table 3). The comparison of actinomycin D, azetomycin I, and actinomycin pip 1β antitumor data shows that thus far none has an advantage over the other and thus the comparative toxicity data becomes the crucial factor on whether one of the analogs is developed towards clinical trials.

Table 3. Typical activities of actinomycin derivatives in murine tumor systems[a]

Tumor	Actinomycin D NSC-3053		Actinomycin pip 1β NSC-107660		Azetomycin I NSC-244392		Actinomysin S_3 NSC-296940	
	% T/C	O.D.[b]	% T/C	O.D.[b]	% T/C	O.D.[b]	% T/C	O.D.[b]
PS31 P388 lymphocytic leukemia	279	100	205	400	266	50	72	10
LE21 L1210 lymphoid leukemia	158	60	159	750	151	300	[115][c]	20
B132 B16 melanocarcinoma	200	25	166	1100	152	75	186	10
C631 Colon 26	153	500	184	2880	157	750	–[d]	–[d]
C872 Colon 38	22	300	9	4500	27	1200	[110][c]	20
CD72 $CD8F_1$ mammary tumor	0	300	1	3000	0	600	36	5

[a] Data are typical for each system and testing is not in direct comparison
[b] O.D., optimal dose in micrograms/kg/inj
[c] [ ], activity criteria not met in this system
[d] –, not tested

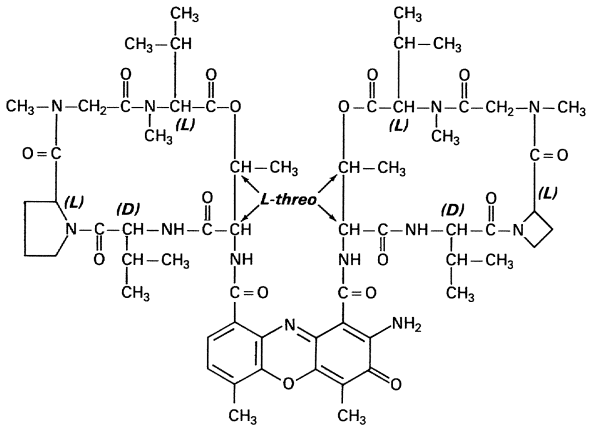

Fig. 2. Structure of azetomycin 1 (NSC 244392)

Pepleomycin (NSC-276382). Many bleomycins have been tested by NCI and in Japan. In the last 18 months the Japanese have renewed NCI's interest in the bleomycins by presenting to NCI their data on several bleomycin analogs including pepleomycin and bleomycin BAPP (Figs. 3 and 4). Pepleomycin (Fig. 3), developed in Japan, differs from bleomycin in the terminal amine group. According to the Japanese data this drug shows less pulmonary toxicity in human clinical trials than does bleomycin, which would make this a second generation drug (less toxicity but equal activity) [22]. This drug is awaiting completion of pulmonary toxicity tests and tumor panel evaluation at NCI in direct comparison with bleomycin, and if results are favorable will be presented to DN late in 1979. Table 4 shows the data obtained with the various bleomycins that are presently of interest to NCI.

Bleomycin BAPP (NSC-294979) (Fig. 4) is another fermentation-derived analog of bleomycin that shows less pulmonary toxicity than bleomycin in the mouse test [22].

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