Reviews

Natural Products in Drug Discovery and Development

Gordon M. Cragg, David J. Newman,* and Kenneth M. Snader

Natural Products Branch, Developmental Therapeutics Program, Division of Cancer Treatment, Diagnosis and Centers, National Cancer Institute, Frederick Cancer Research and Development Center, P.O. Box B, Frederick, Maryland 21702-1201

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Analysis of the number and sources of anticancer and antiinfective agents, reported mainly in *Annual Reports of Medicinal Chemistry* from 1984 to 1995, indicates that over 60% of the approved drugs and pre-NDA candidates (for the period 1989−1995), excluding biologics, developed in these disease areas are of natural origin. Drugs of natural origin have been classified as original natural products, products derived semisynthetically from natural products, or synthetic products based on natural product models. This review highlights the invaluable role that natural products have played, and continue to play, in the drug discovery process, particularly in the areas of cancer and infectious diseases.

While it is common for natural product scientists to claim that natural products form the basis for many of the drugs currently in commercial use or in development, little comprehensive data have been presented to support such claims since Farnsworth and Morris reported their analysis of National Prescription Audit data for the 15-year period 1959−1973;[1] they reported that over 25% of U.S. prescriptions dispensed in 1973 contained active ingredients derived from plants, while 13.3% and 2.7% were derived from microbial and animal sources, respectively. The role of natural products from all sources in drug discovery has been reviewed recently,[2] and one volume has been devoted exclusively to the anticancer area.[3] More comprehensive coverage has been given to plants over the past 10 years (e.g., refs 4−7). Thus, Farnsworth *et al.* have reported that at least 119 compounds derived from 90 plant species can be considered as important drugs currently in use in one or more countries, with 77% of these being derived from plants used in traditional medicine.[7] Further evidence of the importance of natural products is provided by the fact that close to half of the best selling pharmaceuticals in 1991 were either natural products or their derivatives.[8]

Over the past 10 years, there has been a resurgence of interest in the investigation of natural materials as a source of potential, new chemotherapeutic agents, but there are now signs that this interest is once more waning in favor of new approaches to drug discovery, such as combinatorial chemistry and computer-based molecular modeling designs. In order to provide a more solid basis for the claims made for the importance of natural products in drug discovery and development, data on new drugs approved by either the United States Food and Drug Administration (FDA) or comparable entities in other countries, and reported mainly in the *Annual Reports of Medicinal Chemistry* for the years 1983−1994,[9−20] have been analyzed, predominantly in the areas of cancer and infectious diseases. Other data from a variety of sources have also been analyzed covering potential anticancer compounds reported to be in the pre-New Drug Application (NDA) phase up to the end of 1995.

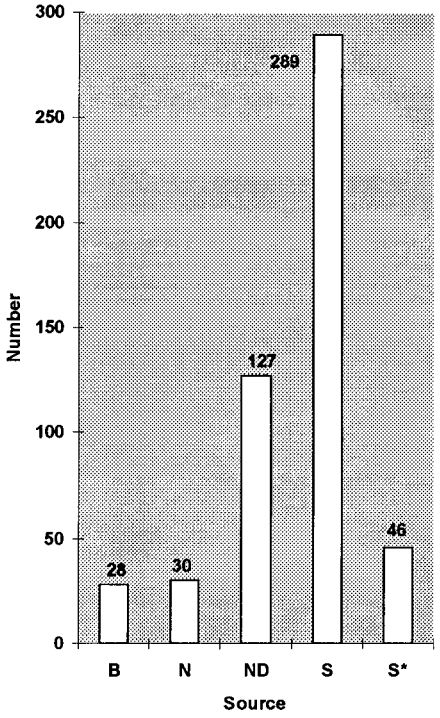

Figure 1. New approved drugs: 1983−1994.

Results

The data have been analyzed in terms of numbers, classified according to their origin as indicated below:

B: Biologics (vaccines, monoclonals, etc. derived from mammalian sources).

N: Derived from an unmodified natural product source.

ND: Derived from a natural product source (e.g., semisynthetics).

S: Exclusively from a synthetic source.

S*: From a synthetic source, but originally modeled on a natural product parent.

The assignment of the designator S* is based on evidence presented by authorities in the field.[21] Thus,

* To whom correspondence should be addressed. Phone: (301)846-5387. Fax: (301)846-6178.

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Table 1. New Approved Drugs: 1983−1994

disease indication[a]	origin of drug[b] B	N	ND	S	S*	refs
analgesic				12		9−13, 16, 17
antiallergic			1	5		12, 13, 16, 18−20
antiarrhythmic				6	1	11, 13,16, 17, 20
antibacterial		6	44	14		9−20
anticancer and adjuvants	6	4	11	12	4	9−20
anticonvulsant				5		11, 15 ,16
antidepressant				16		9, 10, 12, 15−17, 20
antidiabetic		2		2		15, 16, 18, 20
antiemetic			1	3		16−18, 20
antifungal				16		9−14, 17−20
antiglaucoma			2	1	2	9, 11, 13, 14, 20
antihistamine				8		9, 12−14, 16, 17
antihypertensive				27	25	9−20
antiinflammatory	1		12	27		9−20
antithrombotic	2		3	5		10, 13, 14, 16, 17
antiulcer		1	9	11		10−16, 18−20
antiviral				3	7	13−15, 17−20
anxiolytic				7		10−13, 17
bronchodilator			2		4	12, 16
calcium regulator			1	4		12, 13, 15, 17
cardiostimulant				9		10, 14−16, 18, 20
hormone			4			10, 12, 13, 16
hypnotic				10		9−12, 14, 15, 19
hypocholesterolemic		2	1	1		9, 10, 13, 14
hypolipidemic		1		6		9, 11, 12, 20
immunostimulant	2	3	1	1		12, 13, 16, 17, 19, 20
immunosuppressant	1	2	1		1	9, 10, 12, 19, 20
miscellaneous[c]	16	8	26	62	2	9−20
muscle relaxant				5		9, 10, 17, 18
neuroleptic				4		10, 17, 19
nootropic		1	1	6		12−14, 16
platelet aggregation inhibitor			3	1		9, 18, 19
progestogen			4			9, 12, 13
TOTAL (520)	28	30	127	289	46	

[a] As reported in the *Annual Reports of Medicinal Chemistry*, Vols. 19−30 (refs 9−20). Details of generic names, chemical classes, years of introduction, and specific references are available as Supporting Information from the author. [b] B = biologic; N = unmodified natural product; ND = derived from a natural product; S = synthetic; S* = synthetic modeled on a natural product parent. [c] Miscellaneous = disease indications with three or less drugs approved from 1983−1994, including abortifacient, alcohol deterrent, 5-alpha-reductase inhibition, Alzheimer's disease, anabolic, analeptic, anesthetic, antiacne, antianginal, antiasthmatic, anticholelithogenic, anticoagulant, antidiarrheal, antiepileptic, antiestrogen, antifolate, antilipidemic, antimalarial, antimigraine, antinauseant, antiparasitic, anti-Parkinsonian, antiperistaltic, antiprogestogen, antiprolactin, antiprostatic hypertrophy, antipsoriatic, antipsychotic, antirheumatic, antisecretory, antiseptic, antispasmodic, antitussive, benzodiazepine antagonist, cardiac stimulant, cardioprotective, cardiotonic, cerebral vasodilator, chelator, choloretic, chrysotherapeutic, cognition enhancer, coronary vasodilator, cystic fibrosis, diuretic, enzyme, gastroprokinetic, Gaucher's disease, growth hormone, hematopoietic, hemostatic, hepatoprotective, hyperphenylalaninemia, hyperprolactinemia, hypertensive, hypoammonuric, hypocalciuric, hypoglycemia, idiopathic hypersomnia, immunomodulator, B-lactamase inhibitor, lung surfactant, mucolytic, multiple sclerosis, narcotic antagonist, nasal decongestant, neuromuscular blocker, osteoporosis, *P. carinii* pneumonia, precocious puberty, protease inhibitor, psychostimulant, respiratory surfactant, thrombolytic, urolithiasis, urologic, vasodilator, vasoprotective, wound healing.

the peptidic ACE inhibitors (e.g., captopril, enalpril) are modeled on the biologically active peptides (e.g., teprotide) found in the venom of the pit viper, *Bothrops jararaca*, while the antiasthma adrenergic agents (e.g., salbutamol, salmeterol) are modeled on the plant product, ephedrine, isolated from Chinese medicinal plants (e.g., *Ephedra sinica;* "Ma Huang"). Nucleosides are considered as being based on natural product models, while the anticancer drug, mitoxantrone, combines the key features of the anthracyclines and anthracenediones.[22]

The data are presented in the form of bar graphs and tables for the following categories:

- New Approved Drugs: 1983−1994 (Figure 1, Table 1)
- Available Anticancer Drugs: Through 1994 (Figure 2, Table 2)
- Pre NDA Anticancer Drugs: 1989−1995 (Figure 3, Table 3)
- New Approved Anti-Infective Drugs: 1983−1994 (Figure 4, Table 4)

The data shown in the figures and tables listed above highlight the invaluable role that natural products have played, and continue to play, in the drug discovery process related to all disease types (Figure 1; Table 1) and, in particular, in the areas of cancer (Figure 2; Table 2) and infectious diseases (Figure 4; Table 4). In addition, selected structures demonstrating some of these points are presented in Figure 5.

Of the new approved drugs reported between 1983 and 1994 (Table 1),[9−20] drugs of natural origin (N and ND) predominate (78%) in the area of antibacterials, while 61% of the 31 anticancer drugs (excluding the six biologics) are naturally-derived (N and ND) or are modeled on a natural product parent (S*). On the other hand, analgesic, antidepressant, antihistamine, anxiolytic, cardiotonic, and hypnotic drugs, together with the antifungal agents, are exclusively synthetic in origin,

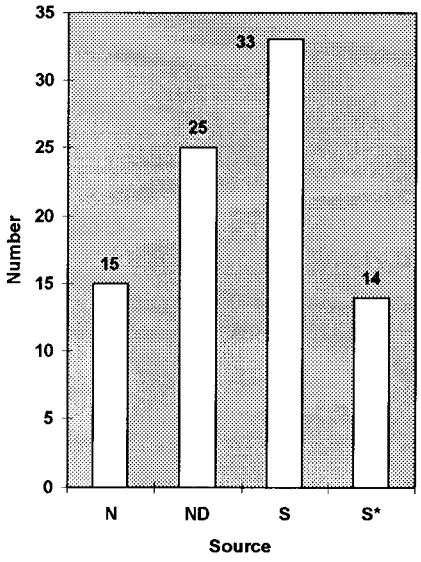

Figure 2. Available anticancer drugs: through 1994.

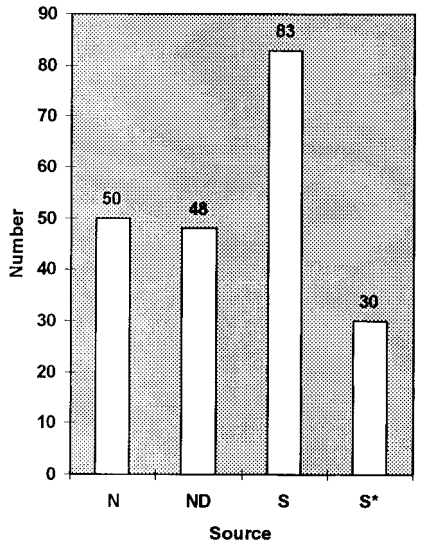

Figure 3. Pre-NDA anticancer drugs: 1989−1995.

while 67.5% of the antiinflammatory drugs are synthetic. Of the 52 antihypertensive drugs, 52% are synthetics and 48% are synthetics modeled on natural product parents. Those disease indications for which three or less drugs were approved have been classed as miscellaneous in Table 1 and are comprised of a majority (54%) of synthetic agents.

Of the 87 approved anticancer drugs (Table 2, excluding the six biologics), 62% are of natural origin or are modeled on natural product parents. Fifteen are the original natural product (two animal-, eight microbial-, and four plant-derived; one steroidal), and 25 are semisynthetic derivatives (14 steroidal; two nucleosides; four microbial- and three plant-derived; one choline and one peptide derivative), while 14 may be classified as being based on a natural product model (S*).

Of the 299 pre-NDA anticancer drug candidates (i.e., in preclinical or clinical development for the period 1989−1995) (Table 3), 50 are the original natural product (nine marine-, 32 microbial-, and nine plant-derived) and 48 are semisynthetic derivatives (two nucleosides, two animal-, 24 microbial-, and 20 plant-derived), while 30 are based on natural product models (S*) and 88 are biologics. The percentage of those drugs having a natural origin, excluding the biologics (where a considerable number are modified monoclonal antibodies), is 61%. These nonbiological 211 pre-NDA anticancer drug candidates include 46 candidates that have been approved by the National Cancer Institute's Decision Network Committee[27] for preclinical and clinical development. Of these compounds, 15 are actual natural products (seven marine-, four microbial-, and four plant-derived), and 13 are semisynthetic derivatives (10 microbial- and three plant-derived), with six based on a natural product model (S*), the remainder being synthetic in origin.

Table 2. Available Anticancer Drugs through 1994

generic name	ref	generic name	ref
Compound Source = B			
interferon, γ-la	18	filgastrim, recombinant	17
interleukin-2	15	nartograstrim	20
pegaspargase	20	sargramostim	17
			no. = 6
Compound Source = N			
actinomycin D	38	paclitaxel	19
asparaginase	38	pentostatin	18
bleomycin	38	streptozocin	38
daunomycin	38	testosterone	38
doxorubicin	38	vinblastine	38
masoprocol	18	vincristine	38
mithramycin	38	angiotensin II	20
mitomycin c	38		
			no. = 15
Compound Source = ND			
cladribine	19	megestrol acetate	38
cytarabine ocfosfate	19	methylprednisolone	38
dromostanolone	38	methyltestosterone	38
epirubicin HCI	10	miltefosine	19
estramustine	38	pirarubicin	14
ethinyl estradiol	38	prednisolone	38
etoposide	38	prednisone	38
fluoxymesterone	38	testolactone	38
formestane	19	triamcinolone	38
hydroxyprogesterone	38	vinorelbine	15
idarubicin hydrochloride	16	zinostatin stimalamer	20
irinotecan hydrochloride	20	leuprolide acetate	10
medroxyprogesterone acetate	38		
			no. = 25
Compound Source = S			
amsacrine	13	levamisole	38
bisantrene hydrochloride	16	lomustine	38
busulfan	38	lonidamine	13
camostat mesylate	11	mechlorethamine	38
carboplatin	12	melphalan	38
carmustine	38	mitotane	38
chlorambucil	38	nilutamide	13
chlorotrianisene	38	pipobroman	38
cis-diamminedichloroplatinum	38	porfimer sodium	19
cyclophosphamide	38	procarbazine	38
dacarbazine	38	ranimustine	13
diethylstilbestrol	38	sobuzoxane	20
flutamide	9	thiotepa	38
fotemustine	15	toremifene	15
hexamethylmelamine	38	triethylenemelamine	38
hydroxyurea	38	uracil mustard	38
ifosfamide	38		
			no. = 33
Compound Source = S*			
aminoglutethimide	38	goserelin acetate	38
cytosine arabinoside	38	leuprolide	38
doxifluridine	13	mercaptopurine	38
enocitabine	9	methotrexate	38
floxuridine	38	mitoxantrone HCI	10
fludarabine phosphate	17	tamoxifen	38
fluorouracil	38	thioguanine	38
			no. = 14

Table 3. Pre NDA Anticancer Drugs 1989−1995

generic name	ref	generic name	ref
		Compound Source = B	
ACC-EL-2 (GTI)/TH,/IL-2	28	MART-1 vaccine	28
ACC-TNF gene (Chiron)/TEL/IL-2	28	MoAb: 3AI,95-549,95-6-22	28
ACC-TNF gene (GTI)/TEL/I]L-2	28	MoAb: 528	28
ADA TRND T-Lymphs	28	MoAb: 90Y-T101	28
ADA TRND umbilicl CD	28	MoAb: B3(1B4M-DTPA)	28
alvac-CEA-vaccine	28	MoAb: B4bR immunotoxin	28
anti-CD3 Act. Lymphocytes	28	MoAb: bombesin (2A11)	28
anti-TAC(Fv)-PE38	27	MoAb: CC49 (Dow)	28
antineoplastons AIO/AS2	28	MoAb: CC49/218sFv	28
auto CD3/CD8 TIL/I]L-2	28	MoAb: COLL (Dow)	28
B7 transfected melanoma vaccine	28	MoAb: chimeric 14.18	28
CM-101	27	MoAb: D612 Abbott Bio	28
CSF-G (Amgen)	28	MoAb: HD37	28
CSF-GM (H)/yeast	28	MoAb: Lmm-1 immunotoxin	28
CSF-GM (Sandoz)	28	MoAb: Lu-CC49	28
CSF-GM (Schering)	28	MoAb: Lym-1*	28
carboxypeptidase G-2	27	MoAb: N901-bR immunotoxin	28
E2.3 & A27.15	27	MoAb: OKT, (T cell)	28
erythropoietin (Ortho)	28	MoAb: R24	28
ID-KLH vaccine (KWAKS)	28	MoAb: R24/GM-CSF(H)	28
ID-KLH/SAF-1	28	MoAb: T90Y/111 in CC49	28
IFN: (Serono)	28	MoAb: 14G2A	28
IFN: Rec alpha 2(Schering)	28	MoAb: XomaZyme-H65 T-cell ricin	28
IFN: Rec gamma (Genentech)	28	N2-transduce TIL	28
IFN: Rec Hu Rec (Ber)	28	PBSC trans gene ADA	28
IFN: Rec leukocyte A (HLR)	28	PEG IL-2 (Chiron)	28
IL-1 Alpha (Dianippon)	28	PEG-asparaginase (K-H)	28
IL-1 Alpha (Dia)/IL-2 (HLR)	28	PIXY (fusion protein)	27
IL-2/A-LAK (Chiron)	28	RAS detox vaccine	28
IL-2/LAK (Chiron)	28	Rh GH/rh IGF-I	28
IL-2/LAK (HLR)	28	TGF-B2 (Celtrix)	28
IL-2/OKT-3-LAK (HLR)	28	TIL-SSTNF TRND 11	28
IL-2/TIL (Cetus, biorector exp.)	28	TNF (Chiron)	28
IL-2/TIL (Chiron)	28	TNF (Genentech)	28
IL-2/TIL (HLR)	28	TNF (Knoll)	28
IL-3 (Sandoz)	28	TNF-transduced TIL (I)	28
IL-3 (Sz)w/GM-CSF	28	TNF-transduced TIL (Chiron)	28
IL-4 (Schering)	28	TRND BM/PBSC w/SCF/DL-3 [IL-6	28
IL-6 (Sandoz)	28	TRND BM/PBSC w/SCI'EL-3	28
IL-6 (Serono)	28	TRND TEL PBL + EL-2/IF'N	28
LMIB-7 immunotoxin	28	vaccine/RAS-P53	28
LN6 vector: GIN vector: EL-2/TIL	28	vaccinia-CEA vaccine	28
MAGE-1 vaccine	28	xomazyme-H65	27
MAGE-3 vaccine	28	zoladex (LHRF)	28
			no. = 88
		Compound Source = N	
15-deoxyspergualin	25	girolline	23
2,3-dihydroxybenzoic acid	23	gliotoxin	25
9-*cis*-retinoic acid	27	halichondrin B	27
acetoxycycloheximide	23	halomon	27
acivicin	38	homoharringtonine	38
aclacinomycin	38	IST-622	22
aeroplysinin-1	24	ipomeanol	27
bryostatin 1	27	jasplakinolide	27
calphostin C	23	L-alanosine	27
chaetomellic acid	25	manumycin	25
clerocidin	22	menogaril	38
cordycepin/deoxycoformycin	27	pepticinnamin E	25
cucurbitacin E	27	perillyl alcohol	27
cycloheximide	23	porfiromycin	38
didemnin B	38	pyrindamycins	22
dolastatin 10	27	rapamycin	22
dolastatin 11	27	rhizoxin	22
duocarmycin	22	saintopin	22
echinomycin	38	sangivamycin	23
ecteinascidin 743	27	terpentecin	22
elsamicin A	23	thymidine	28
fostriecin	23	*trans*-retinoic acid (ATRA)	28
fumagillin	24	UCN-01	27
geldanamycin	27	UCT4B	22
genistein	24	zaragozic acid	25
			no. = 50
		Compound Source = ND	
13-*cis*-retinoic acid	26	ilmofosine	22
4′-I′4′-deshydroxydoxorubicin	23	intolpicin	22

Table 3. (Continued)

generic name	ref	generic name	ref
		Compound Source = ND (Continued)	
4-HCR	26	KRN-8602	23
6-aminonicotinamide	27	KT6528	22
9-aminocamptothecin (9-AC)	28	KW2149	22
AGM-1470	24	LGD 1069	26
aphidicolin glycinate	23	LY188011	23
bizelesin	27	lavendustin A, methyl ester	24
breflate	27	lovastatin (mevacor)	28
butyric acid and tributyrin	27	NK611	22
CPT-11 (monotecan)	28	PSC 833	27
DBD (dibromodulcitol)	28	pentosan	28
DX-52-1 (quinocarmycin analog)	27	photofrin II	28
datelliptium	22	rebeccamycin analogue	27
depsipeptide	27	retelliptine	22
doxorubicin [liposomal]	27	SM-5887	23
ED-110	22	SUN4599	23
enediynes	22	spicamycin analogue	27
erbstatin (tyrphostin)	24	TNP-470	27
etopophos	22	taxotere	27
etretinate	26	thymopentin (thymopoietin)	28
FCE24517	22	topotecan (hycamptamine)	38
fenretinide	26	VM-26 (teniposide)	28
flavopiridol	27	VP-16	28
			no. = 48
		Compound Source = S	
10-EDAM/edatrexate	22	levamisole	28
1843U89	22	lometrexol	22
AZQ (diaziquone)	28	MDR-1	28
aminothiadiazole (ATDA)	28	MECCNU (methyl-CCNU)	28
amonafide	23	MGBG (methyl-G)	28
B-581	25	mafosfamide L-lysine	28
BSO	27	merbarone	23
BW502U	23	mesna	28
BW770U	23	methylglyoxal bis-guanylhydrazone	38
BW773U	23	*N*-methylformamide	38
BZA-2B	25	NC-190	23
BZA-5B	25	ormaplatin	28
batracyclin	23	PALA	28
benzoylphenylureas	27	PCNU	28
β-cyclodextrin tetradecaSO_4	24	PD 115934	22
CAI	27	PZDH (pyrazine)	28
CI-958	22	Pc-4	27
CI-980	27	penclomedine	27
CIHP (iproplatin)	28	phenylacetic acid	27
CL 286,558	23	phenylbutyrate	28
CL 287,110	23	pibenzimol	38
CP-115,953	22	piroxantrone	38
CQS (chloroquin sulphon)	28	pyrazinediazohydroxide	38
caracemide	38	pyrazoloacridine	38
carboxyamideaminoimidazole	38	(*R*)-verapamil	28
chloroquinoxalinesulfonamide	38	SR-2508 (etanidazole)	28
clomesome	28	SR95325A	23
DDATHF	23	SU101	27
deazauridine	38	SarCNU	27
FPP-analogue 8	25	spirogermanium	38
FPP-analogue 9	25	spiromustine	38
GPA-1734	24	sulfonobenzoyl nitrostyrenes	24
$GaNO_3$ (gallium nitrate)	28	sulofenur	28
HMBA	38	suramin	24
hepsulfam	27	temozolomide	27
hexamethylmelamine	28	terephthalamidine	38
hydrea (hydroxyurea)	28	teroxirone	38
ICRF 187	28	tetraplatin	27
ifosfamide	28	thiadiazole	38
L-731,734	25	triazinate (TZT)	28
L-731,735	25	WR-2721 (amifostine)	28
leucovorin (PO & IV)	28		
			no. = 83
		Compound Source = S*	
2-chlorodeoxyadenosine	27	fazarabine (Ara-AC)	38
6-MMPR (6-methylMP riboside)	28	gemcitabine	27
6-MT (PO & IV)	28	HDMTX	28
AZT (cancer)	28	ICI D1694	22
azacitidine	27	IUdR	28
azatoxin	22	LY231514	22
biantrazole	23	methylmercaptopurine riboside	38

Table 3 (continued)

generic name	ref	generic name	ref
	Compound Source = S* (Continued)		
bromodeoxyuridine (BUDR)	28	O6-benzylguanine	27
CPE-C	27	oxantrazole	23
DFMO (difluoromethylornithine)	38	TMCA (trimethylcolchicinic acid)	38
DHAC (dihydroazacytidine)	28	TNffX (trimetrexate)	38
dichloromethotrexate	38	thioguanine (6-TG)	38
DuP937	22	tiazofurin	38
DuP941	22	triciribine phosphate	38
DuP942	22	uridine	27
			no. = 30

Since a large number of antiinfective compounds in the pre-NDA stage of development are considered proprietary by commercial corporations, insufficient information was available to present data on these materials. Using the data available for approved drugs from the *Annual Reports of Medicinal Chemistry*, however, the following data were obtained for the years 1983−1994. Of the 93 new approved antiinfectives (Table 4, Figure 4), seven are actual natural products and 45 are semisynthetic derivatives, with seven based on natural product models (S*) and no biologicals, giving a total of 63% of natural origin.

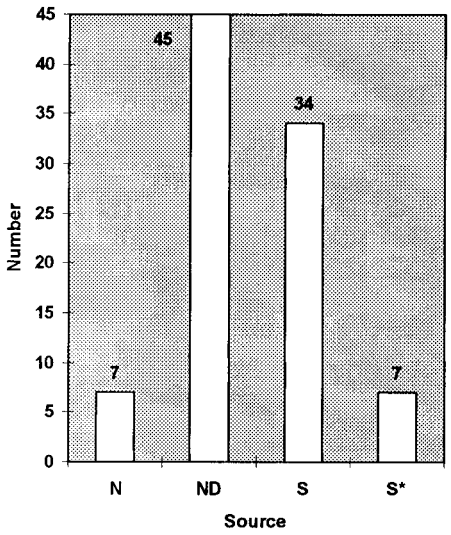

Figure 4. New approved anti-infective drugs: 1983−1994.

Discussion

Widely recognized as being of serious and immediate concern is the crisis of new and reemerging infectious diseases for which no effective therapies are available and the development of resistance of many pathogens to currently used drugs. The urgency of the situation is highlighted by the introduction of the new publication, "Emerging Infectious Diseases", by the National Center for Infectious Diseases of the Centers for Disease Control and Prevention.[29] A similar situation exists with the need to develop new cancer chemotherapeutic agents with activity against the disease-types still

Table 4. New Antiinfective Drugs, 1983−1994

generic name	ref no.	generic name	ref
	Compound Source = N		
drug use = antibacterial			
RV-11	15	miokamycin	11
carumonam	14	mupirocin	11
isepamicin	14	teicoplanin	14
			no. = 6
	Compound Source = ND		
drug use = antibacterial			
arbekacin	16	cefprozil	18
aspoxicillin	13	ceftazidime	9
astromycin sulfate	11	cefteram pivoxil	13
azithromycin	14	ceftibuten	18
aztreonam	10	cefuroxime axetil	13
cefbuperazone sodium	11	cefuzonam sodium	13
cefdinir	17	clarithromycin	16
cefditoren pivoxil	20	dirithromycin	19
cefepime	19	erythromycin acistrate	14
cefetamet pivoxil HCl	18	flomoxef sodium	14
cefixime	13	imipenem/cilastatin	11
cefmenoxime HCl	9	lenampicillin HCl	13
cefminox sodium	13	loracarbef	18
cefodizime sodium	16	meropenem	20
cefonicid sodium	10	panipenem/betamipron	20
ceforanide	10	rifabutin	18
cefotetan disodium	10	rifapentine	14
cefotiam hexetil HCl	17	rifaximin	11
cefpimizole	13	rokitamycin	12
cefpiramide sodium	11	roxithromycin	13
cefpirome sulfate	18	sultamycillin tosylate	13
cefpodoxime proxetil	15	temocillin disodium	10
			no. = 44

Table 4. New Antiinfective Drugs, 1983−1994

generic name	ref no.	generic name	ref
	Compound Source = S		
drug use = antibacterial			
brodimoprin	19	norfloxacin	9
ciprofloxacin	12	ofloxacin	11
enoxacin	12	pefloxacin mesylate	11
fleroxacin	18	rufloxacin hydrochloride	18
levofloxacin	19	sparfloxacin	19
lomefloxacin	15	temafloxacin hydrochloride	17
nadifloxacin	19	tosufloxacin	16
			no. = 14
drug use = antifungal			
amorolfine hydrochloride	17	naftifine HCl	10
butenafine hydrochloride	18	neticonazole HCl	19
butoconazole	12	oxiconazole nitrate	9
cloconazole HCl	12	sertaconazole nitrate	18
fenticonazole nitrate	13	sulconizole nitrate	11
fluconazole	14	terbinafine hydrochloride	17
itraconazole	14	terconazole	9
lanoconazole	20	tioconazole	9
			no. = 16
	Compound Source = N		
drug use = antimalarial			
artemisinin	13		
			no. = 1
	Compound Source = ND		
drug use = antimalarial			
mefloquine HCl	11		
			no. = 1
	Compound Source = S		
drug use = antimalarial			
halofantrine	14		
drug use = antiviral			
foscarnet sodium	15	rimantadine HCl	13
propagermanium	20		
			no. = 4
	Compound Source = S*		
drug use = antiviral			
didanosine	17	stavudine	20
famciclovir	20	zalcitabine	18
ganciclovir	14	zidovudine	13
sorivudine	19		
			no. = 7

resistant to current therapies and to overcome the development of multidrug resistance, which is increasingly observed in the treatment of many tumors.

There is an urgent need to identify novel, active chemotypes as leads for effective drug development, and, as was dramatically illustrated by the discovery of the "wonder" antibiotics of the 1940's and 1950's, nature is the prime source of such lead discoveries. It has been estimated that only 5−15% of the approximately 250 000 species of higher plants have been systematically investigated for the presence of bioactive compounds,[30] while the potential of the marine environment has barely been tapped.[31] The Actinomycetes have been extensively investigated and have been, and remain, a major source of novel microbial metabolites,[32] but the potential of these and other microbial sources,[33] particularly those found in extreme environments,[34] seems unbounded. To these natural sources can be added the potential to investigate the rational design of novel structure types within certain classes of microbial metabolites through genetic engineering, as has been elegantly demonstrated with bacterial polyketides.[35]

To expand on Dr. Norman Farnsworth's closing remarks in his guest editorial on "An old source for new drugs" in the August 1995 issue of *Pharmaceutical Technology*, "The world of plants, **and indeed all natural sources** (authors' addition), represents a virtually untapped reservoir of novel drugs awaiting imaginative and progressive organizations."[36] Furthermore, in the words of Dr. Dennis Pirages, Director of the Harrison Center on the Future Global Agenda at the University of Maryland, "infectious diseases are potentially the largest threat to human security lurking in the post-cold war world".[37] Coupled with the continuing threat to biodiversity through the destruction of terrestrial and marine ecosystems and the proven record of natural products in drug discovery, this statement provides a compelling argument for **expanding**, not decreasing, the exploration of nature as a source of novel active agents.

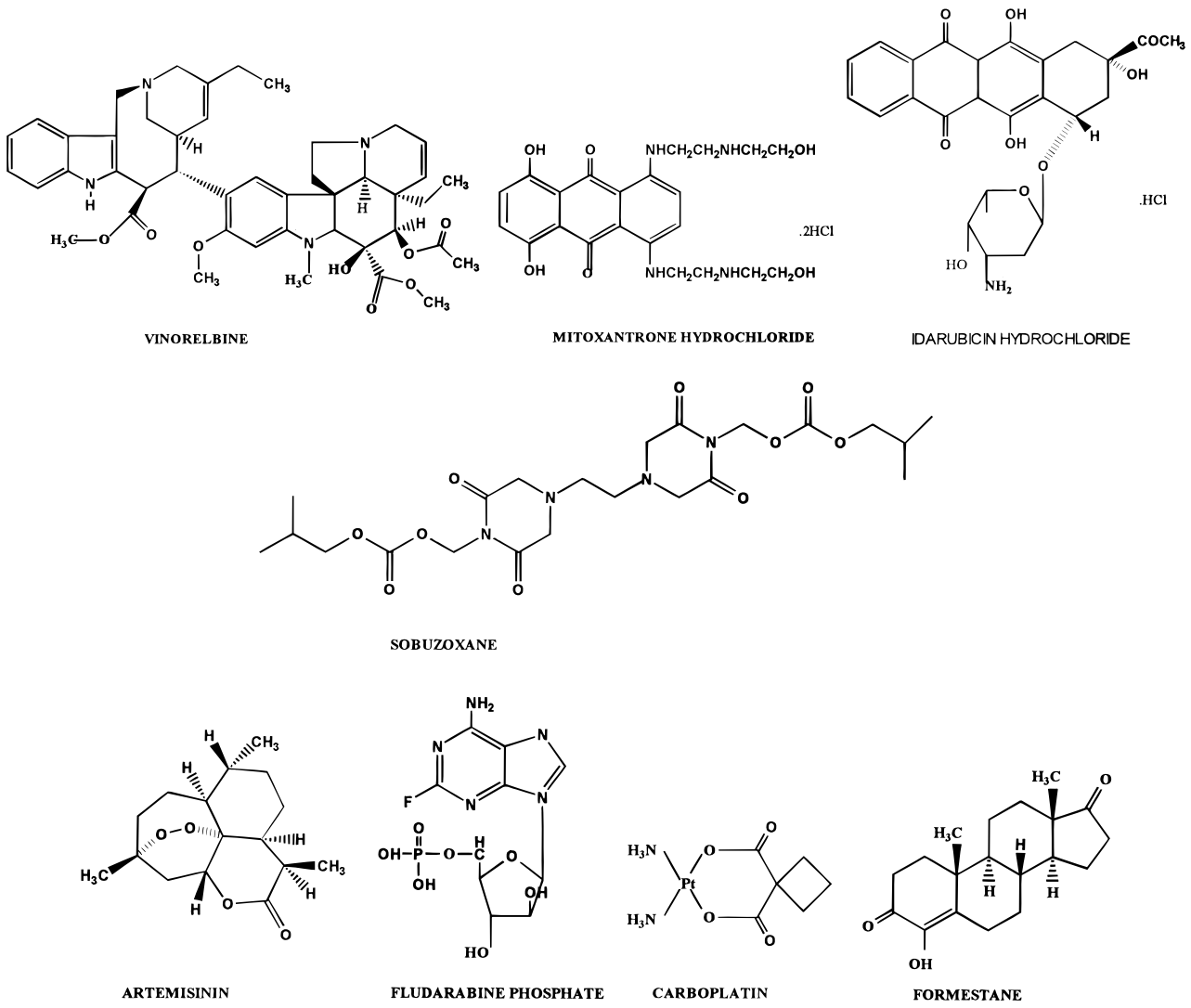

Figure 5. Selected structures.

Supporting Information Available: Supporting Information in the form of a table listing individual drugs by generic name, chemical class, disease indication, source (e.g., B, N, ND, etc.), and reference [*Annual Reports of Medicinal Chemistry*, Vols. 19−30 (9−20); *Current Therapy in Oncology* (38); and a list of drugs currently undergoing clinical trials under the auspices of the NCI Clinical Therapy Evaluation Program (CTEP)] suitable for photoreproduction is available from the authors.

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(29) Published by the National Center for Infectious Diseases, Centers for Disease Control and Prevention (CDC), 1600 Clifton Road, Mallstop C-12, Atlanta, GA 30333. Fax: (404)639-3039. E-mail: eideditor@cidodl.em.cdc.gov.
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