Natural Products as Sources of New Drugs over the Last 25 Years[⊥]

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This review is an updated and expanded version of two prior reviews that were published in this journal in 1997 and 2003. In the case of all approved agents the time frame has been extended to include the 25½ years from 01/1981 to 06/2006 for all diseases worldwide and from 1950 (earliest so far identified) to 06/2006 for all approved antitumor drugs worldwide. We have continued to utilize our secondary subdivision of a "natural product mimic" or "NM" to join the original primary divisions. From the data presented, the utility of natural products as sources of novel structures, but not necessarily the final drug entity, is still alive and well. Thus, in the area of cancer, over the time frame from around the 1940s to date, of the 155 small molecules, 73% are other than "S" (synthetic), with 47% actually being either natural products or directly derived therefrom. In other areas, the influence of natural product structures is quite marked, with, as expected from prior information, the antiinfective area being dependent on natural products and their structures. Although combinatorial chemistry techniques have succeeded as methods of optimizing structures and have, in fact, been used in the optimization of many recently approved agents, we are able to identify only one *de novo* combinatorial compound approved as a drug in this 25 plus year time frame. We wish to draw the attention of readers to the rapidly evolving recognition that a significant number of natural product drugs/leads are actually produced by microbes and/or microbial interactions with the "host from whence it was isolated", and therefore we consider that this area of natural product research should be expanded significantly.

It is over nine years since the publication of our first,[1] and three years since the second,[2] analysis of the sources of new and approved drugs for the treatment of human diseases, both of which indicated that natural products continued to play a highly significant role in the drug discovery and development process.

That this influence of Nature in one guise or another has continued is shown by inspection of the information given below, where with the advantage of now over 25 years of data, we have been able to refine the system, eliminating a few duplicative entries that crept into the original data sets. In particular, as behooves authors from the National Cancer Institute (NCI), in the specific case of cancer treatments, we have gone back to consult the records of the FDA and added to these, comments from investigators who have informed us over the past two years of compounds that may have been approved in other countries and that were not captured in our earlier searches. These cancer data will be presented as a stand-alone section as well as including the last 25 years of data in the overall discussion.

As we mentioned in our 2003 review,[2] the development of high-throughput screens based on molecular targets had led to a demand for the generation of large libraries of compounds to satisfy the enormous capacities of these screens. As we mentioned at that time, the shift away from large combinatorial libraries has continued, with the emphasis now being on small, focused (100 to ~3000) collections that contain much of the "structural aspects" of natural products. Various names have been given to this process, including "Diversity Oriented Syntheses",[3−6] but we prefer to simply say "more natural product-like", in terms of their combinations of heteroatoms and significant numbers of chiral centers within a single molecule,[7] or even "natural product mimics" if they happen to be direct competitive inhibitors of the natural substrate. It should also be pointed out that Lipinski's fifth rule effectively states that the first four rules do not apply to natural products or to any molecule that is recognized by an active transport system when considering "druggable chemical entities".[8−10]

Although combinatorial chemistry in one or more of its manifestations has now been used as a discovery source for approximately 70% of the time covered by this review, to date, we can find only one *de novo* new chemical entity (NCE) reported in the public domain as resulting from this method of chemical discovery and approved for drug use anywhere. This is the antitumor compound known as sorafenib (Nexavar, **1**) from Bayer, approved by the FDA in 2005. It was known during development as BAY-43-9006 and is a multikinase inhibitor, targeting several serine/threonine and receptor tyrosine kinases (RAF kinase, VEGFR-2, VEGFR-3, PDGFR-beta, KIT, and FLT-3) and is in multiple clinical trials as both combination and single-agent therapies at the present time, a common practice once approved for one class of cancer treatment.

As mentioned by the authors in prior reviews on this topic and others, the developmental capability of combinatorial chemistry as a means for structural optimization once an active skeleton has been identified is without par. The expected surge in productivity, however, has not materialized; thus, the number of new active substances (NASs), also known as New Chemical Entities (NCEs), which we consider to encompass all molecules, including biologics and vaccines, from our data set hit a 24-year low of 25 in 2004 (though 28% of these were assigned to the ND category), with a rebound to 54 in 2005, with 24% being N or ND and 37% being biologics (B) or vaccines (V). Fortunately, however, research being conducted by groups such as Danishefsky's, Ganesan's, Nicolaou's, Porco's, Quinn's, Schreiber's, Shair's, Waldmann's, and Wipf's is continuing the modification of active natural product skeletons as leads to novel agents, so in due course, the numbers of materials developed by linking Mother Nature to combinatorial synthetic techniques should increase. This aspect, plus the potential contributions from the utilization of genetic analyses of microbes, will be discussed at the end of this review.

Against this backdrop, we now present an updated analysis of the role of natural products in the drug discovery and development process, dating from 01/1981 through 06/2006. As in our earlier

[⊥] Dedicated to the late Dr. Kenneth L. Rinehart of the University of Illinois at Urbana−Champaign for his pioneering work on bioactive natural products.

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analyses,[1,2] we have consulted the *Annual Reports of Medicinal Chemistry*, in this case from 1984 to 2005,[11−32] and have produced a more comprehensive coverage of the 1981−2006 time frame through addition of data from the publication *Drug News and Perspective*[33−49] and searches of the Prous *Integrity* database, as well as by including information from individual investigators. We also updated the biologicals section of the data set using information culled from disparate sources that culminated in a recent review (2005) on biopharmaceutical drugs.[50]

We have also included relevant references in a condensed form in Tables 1−5, 8, and 9; otherwise the numbers of references cited in the review would become overwhelming. In these cases, "ARMC ##" refers to the volume of *Annual Reports in Medicinal Chemistry* together with the page on which the structure(s) can be found. Similarly, "DNP ##" refers to the volume of *Drug News and Perspective* and the corresponding page(s), and an "I ######" is the accession number in the Prous *Integrity* database. Finally, we have used "Boyd" to refer to a review article[51] on clinical antitumor agents and "M'dale" to refer to *Martindale*[52] with the relevant page noted.

It should be noted that the "Year" header in all tables is the "Year of Introduction" of the drug. In some cases there are discrepancies between sources as to the actual year due to differences in definitions. We have generally taken the earliest year in the absence of further information.

Results

As before, we have covered only New Chemical Entities (NCEs) in the present analysis. If one reads the FDA and PhRMA Web sites, the numbers of NDA approvals are in the high tens to low hundred numbers for the last few years. If, however, one removes combinations of older drugs and old drugs with new indications, and/or improved delivery systems, then the number of true NCEs is only in the 20s to just over 50 per year for the last five or so years (see Figures 2 and 5).

As in our earlier analyses,[1,2] the data have been analyzed in terms of numbers and classified according to their origin using both the previous major categories and their subdivisions.

Major Categories of Sources. The major categories used are as follows:

"B" Biological; usually a large (>45 residues) peptide or protein either isolated from an organism/cell line or produced by biotechnological means in a surrogate host.

"N" Natural product.

"ND" Derived from a natural product and is usually a semisynthetic modification.

"S" Totally synthetic drug, often found by random screening/modification of an existing agent.

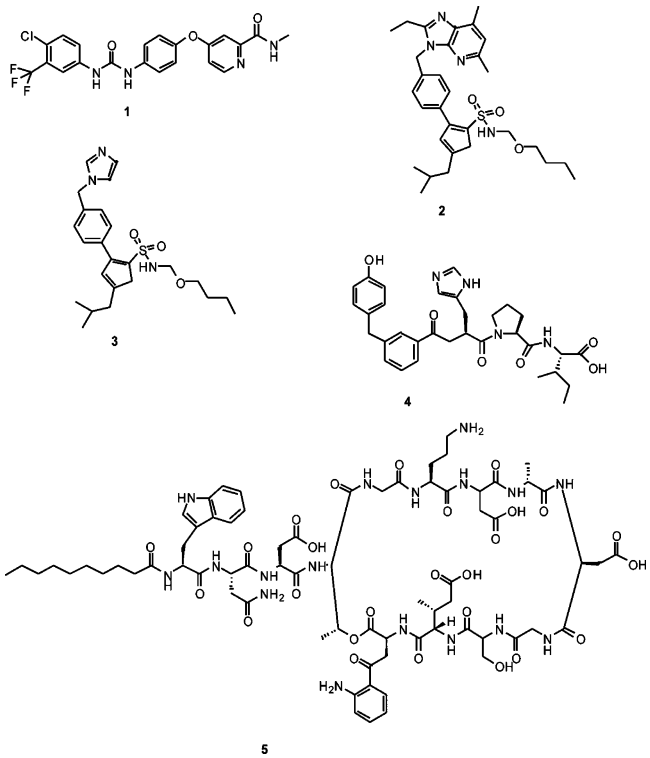
"S*" Made by total synthesis, but the pharmacophore is/was from a natural product.

"V" Vaccine.

Subcategory. "NM" Natural product mimic (see rationale and examples below).

(For amplification as to the rationales used for categorizing using the above subdivisions, the reader should consult the earlier reviews.[1,2])

In the field of anticancer therapy, the advent in 2001 of Gleevec, a protein tyrosine kinase inhibitor, was justly heralded as a breakthrough in the treatment of leukemia. This compound was classified as an "NM" on the basis of its competitive displacement of the natural substrate ATP, whose intracellular concentrations can approach 5 mM. We have continued to classify PTK and other kinase inhibitors that are approved as drugs under the "/NM" category for exactly the same reasons as elaborated in the 2003 review[2] and have continued to extend it to cover other direct inhibitors/antagonists of the natural substrate/receptor interaction whether obtained by direct experiment or by *in silico* studies followed by direct assay in the relevant system. Similarly, a number of new peptidic drug entities, though formally synthetic in nature, are simply produced by synthetic methods rather than by the use of fermentation or extraction. In some cases, an end group might have been changed for ease of recovery. In addition, a number of compounds produced totally by synthesis are, in fact, isosteres of the peptidic substrate and are thus "natural product mimics" in the truest sense of the term. For further information on this area, interested readers should consult the excellent review by Hruby.[53]



As an example of what can be found by studies around relatively simple peptidomimics of the angiotensin II structure, the recent paper of Wan et al.[54] demonstrating the modification of the known but nonselective AT_1/AT_2 agonist L-162313 (**2**, itself related to the sartans) into the highly selective AT_2 agonist (**3**) (a peptidomimetic structure) led to the very recent identification of short pseudopeptides exemplified by **4**, which is equipotent (binding affinity = 500 pM) with angiotensin II and has a better than 20 000-fold selectivity versus AT_1, whereas angiotensin II has only a 5-fold binding selectivity in the same assay.[55] It will be interesting to see if any compounds such as these will end up as cardiovascular agents since it has been demonstrated that activation of the AT_2 receptor affects cardiac remodeling and leads to reduced blood pressure.[56]

In the area of modifications of natural products by combinatorial methods to produce entirely different compounds that may bear little if any resemblance to the original, but are legitimately assignable to the "NM" category, citations are given in previous reviews.[3,57−64] In addition, one should consult the recent reports from Waldmann's group[65,66] and those by Ganesan,[67] Shang and Tan,[68] Constantino,[69] and Violette et al.[70] on the use of privileged structures as skeletons around which to build libraries. Another paper of interest in this regard is the editorial by Macarron from GSK,[9] as this may be the first time where data from industry on the results of HTS screens of combichem libraries versus potential targets were reported with a discussion of lead discovery rates. In this paper, Macarron reemphasizes the fifth Lipinski rule, which is often ignored; "natural products do not obey the other four".

Table 1. New Chemical Entities and Medical Indications by Source of Compound 01/1981−06/2006[a,b]

		origin of drug							
indication	total	B	N	ND	S	S/NM	S*	S*/NM	V
analgesic	16		1		11	2	2		
anesthetic	5				5				
anti-Alzheimer's	4		1			3			
anti-Parkinsonism	12			2	1	5		4	
antiallergic	16		1	3	12				
antianginal	5				5				
antiarrhythmic	16		1		13			2	
antiarthritic	15	5		1	3	6			
antiasthmatic	14	1		3	2	6		2	
antibacterial	109		10	64	23			1	11
anticancer	100	17	9	25	18	12	11	6	2
anticoagulant	17	4		12			1		
antidepressant	22				7	13		2	
antidiabetic	32	18	1	4	4	4	1		
antiemetic	10				1	1		8	
antiepileptic	11			2	6		2	1	
antifungal	29	1		3	22	3			
antiglaucoma	13			4		5	1	3	
antihistamine	12				12				
antihyperprolactinemia	4			4					
antihypertensive	77			2	27	14	2	32	
antiinflammatory	51	1		13	37				
antimigraine	10				2	1		7	
antiobesity	4			1		3			
antiparasitic	14		2	5	4		2		1
antipsoriatic	7	2		3			1	1	
antipsychotic	7				3	2		2	
antithrombotic	28	13	1	5	2	5		2	
antiulcer	32	1	1	12	18				
antiviral	78	12		2	7	1	20	11	25
anxiolytic	10				8	2			
benign prostatic hypertrophy	4		1	1	1	1			
bronchodilator	8			2				6	
calcium metabolism	17			8	8	1			
cardiotonic	13			3	2	3		5	
chelator & antidote	5				4	1			
contraception	7			7					
diuretic	5				4	1			
gastroprokinetic	4				1	2		1	
hematopoiesis	6	6							
hemophilia	11	11							
hormone	22	12		10					
hormone replacement therapy	8			8					
hypnotic	12				12				
hypocholesterolemic	11		3	1	2			5	
hypolipidemic	8		1		7				
immunomodulator	4	2	1	1					
immunostimulant	10	4	3	2	1				
immunosuppressant	12	4	5	3					
male sexual dysfunction	4							4	
multiple sclerosis	4	3					1		
muscle relaxant	10			4	2	1	3		
neuroleptic	9				1	6		2	
nootropic	8			3	5				
osteoporosis	4	2		1	1				
platelet aggregation inhibitor	4			3		1			
respiratory distress syndrome	6	3	1		1	1			
urinary incontinence	4				2	2			
vasodilator	5			3	2				
vulnerary	5	2		2	1				
grand total	1010	124	43	232	310	108	47	107	39

[a] Where there were ≤ 3 NCEs per indication in the time frame 01/1981−06/2006, the number of NCEs totaled 174. These were assignable as B, 41; N, 12; ND, 38; S, 54; S/NM, 10; S*, 5; S*/NM, 7; V, 7. [b] The indications for these 174 drugs are as follows: 5 alpha-reductase inhibitor, ADHD, CNS stimulant, COPD, Crohn's disease, Fabry's disease, Gaucher's disease, IBS, Lyme disease, MI, acute, MMRC, PCP/toxoplasmosis, Pompe's disease, abortifacient, acromelagy, actinic keratoses, adjuvant/colorectal cancer, alcohol deterrent, anabolic metabolism, analeptic, anemia, angina, anti-sickle cell anemia, antiacne, antiatherosclerotic, anticholelithogenic, anticonvulsant, antidiarrheal, antidote, antiemphysemic, antiestrogenic, antihyperuricemia, antihypotensive, antinarcolepsy, antinarcotic, antinauseant, antiperistaltic, antiprogestogenic, antirheumatic, antisecretory, antisepsis, antiseptic, antispasmodic, antispastic, antitussive, antityrosinaemia, antixerostomia, benzodiazepine antagonist, beta-lactamase inhibitor, blepharospasm, bone disorders, bone morphogenesis, bowel evacuant, cardioprotective, cardiovascular disease, cervical dystonia, chelator, choleretic, chronic idiopathic constipation, cognition enhancer, congestive heart failure, cystic fibrosis, cytoprotective, diabetic foot ulcers, digoxin toxicity, diphtheria-pertussis-tetanus, dysuria, enzyme, erythropoiesis, expectorant, gastroprotectant, genital warts, hematological, hemostatic, hepatoprotectant, hyperammonemia, homocystinuria, hyperparathyroidism, hyperphenylalaninemia, hyperphosphatemia, hypoammonuric, hypocalciuric, hypogonadism, iron chelator, joint lubricant, lipoprotein disorders, macular degeneration, mucolytic, mucopolysaccharidosis, mucositis, myleodysplasia, narcolepsy, nasal decongestant, neuropathic pain, neuroprotective, opiate detoxification, osteoarthritis, ovulation, pancreatic disorders, pancreatitis, pertussis, photosensitizer, pituitary disorders, porphyria, premature birth, progestogen, psychostimulant, purpura fulminans, rattlesnake antivenom, reproduction, restenosis, sclerosant, secondary hyperthryoidism, sedative, skin photodamage, smoking cessation, strabismus, subarachnoid hemorrhage, thrombocytopenia, treatment of GH deficiency, ulcerative colitis, urea cycle disorders, urolithiasis.

Table 2. Antibacterial Drugs from 01/1981 to 06/2006 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	reference	page	source
RV-11	Zalig	1989	ARMC 25	318	N
carumonam	Amasulin	1988	ARMC 24	298	N
daptomycin	Cubicin	2003	ARMC 39	347	N
fosfomycin trometamol	Monuril	1988	I 112334		N
isepamicin	Isepacin	1988	ARMC 24	305	N
micronomicin sulfate	Sagamicin	1982	I 091082		N
miokamycin	Miocamycin	1985	ARMC 21	329	N
mupirocin	Bactroban	1985	ARMC 21	330	N
netilimicin sulfate	Netromicine	1981	I 070366		N
teicoplanin	Targocid	1988	ARMC 24	311	N
apalcillin sodium	Lumota	1982	I 091130		ND
arbekacin	Habekacin	1990	ARMC 26	298	ND
aspoxicillin	Doyle	1987	ARMC 23	328	ND
astromycin sulfate	Fortimicin	1985	ARMC 21	324	ND
azithromycin	Sunamed	1988	ARMC 24	298	ND
aztreonam	Azactam	1984	ARMC 20	315	ND
biapenem	Omegacin	2002	ARMC 38	351	ND
cefbuperazone sodium	Tomiporan	1985	ARMC 21	325	ND
cefcapene pivoxil	Flomox	1997	ARMC 33	330	ND
cefdinir	Cefzon	1991	ARMC 27	323	ND
cefditoren pivoxil	Meiact	1994	ARMC 30	297	ND
cefepime	Maxipime	1993	ARMC 29	334	ND
cefetamet pivoxil HCl	Globocef	1992	ARMC 28	327	ND
cefixime	Cefspan	1987	ARMC 23	329	ND
cefmenoxime HCl	Tacef	1983	ARMC 19	316	ND
cefminox sodium	Meicelin	1987	ARMC 23	330	ND
cefodizime sodium	Neucef	1990	ARMC 26	300	ND
cefonicid sodium	Monocid	1984	ARMC 20	316	ND
cefoperazone sodium	Cefobis	1981	I 127130		ND
ceforanide	Precef	1984	ARMC 20	317	ND
cefoselis	Wincef	1998	ARMC 34	319	ND
cefotetan disodium	Yamatetan	1984	ARMC 20	317	ND
cefotiam HCl	Pansporin	1981	I 091106		ND
cefozopran HCl	Firstcin	1995	ARMC 31	339	ND
cefpimizole	Ajicef	1987	ARMC 23	330	ND
cefpiramide sodium	Sepatren	1985	ARMC 21	325	ND
cefpirome sulfate	Cefrom	1992	ARMC 28	328	ND
cefpodoxime proxetil	Banan	1989	ARMC 25	310	ND
cefprozil	Cefzil	1992	ARMC 28	328	ND
cefsoludin sodium	Takesulin	1981	I 091108		ND
ceftazidime	Fortam	1983	ARMC 19	316	ND
cefteram pivoxil	Tomiron	1987	ARMC 23	330	ND
ceftibuten	Seftem	1992	ARMC 28	329	ND
ceftizoxime sodium	Epocelin	1982	I 070260		ND
ceftriaxone sodium	Rocephin	1982	I 091136		ND
cefuroxime axetil	Zinnat	1987	ARMC 23	331	ND
cefuzonam sodium	Cosmosin	1987	ARMC 23	331	ND
clarithromycin	Klaricid	1990	ARMC 26	302	ND
dalfopristin	Synercid	1999	ARMC 35	338	ND
dirithromycin	Nortron	1993	ARMC 29	336	ND
doripenem	Finibax	2005	DNP 19	42	ND
ertapenem sodium	Invanz	2002	ARMC 38	353	ND
erythromycin acistrate	Erasis	1988	ARMC 24	301	ND
flomoxef sodium	Flumarin	1988	ARMC 24	302	ND
flurithromycin ethylsuccinate	Ritro	1997	ARMC 33	333	ND
fropenam	Farom	1997	ARMC 33	334	ND
imipenem/cilastatin	Zienam	1985	ARMC 21	328	ND
lenampicillin HCI	Varacillin	1987	ARMC 23	336	ND
loracarbef	Lorabid	1992	ARMC 28	333	ND
meropenem	Merrem	1994	ARMC 30	303	ND
moxalactam disodium	Shiomarin	1982	I 070301		ND
panipenem/betamipron	Carbenin	1994	ARMC 30	305	ND
quinupristin	Synercid	1999	ARMC 35	338	ND
rifabutin	Mycobutin	1992	ARMC 28	335	ND
rifamixin	Normix	1987	ARMC 23	341	ND
rifapentine	Rifampin	1988	ARMC 24	310	ND
rifaximin	Rifacol	1985	ARMC 21	332	ND
rokitamycin	Ricamycin	1986	ARMC 22	325	ND
roxithromycin	Rulid	1987	ARMC 23	342	ND
sultamycillin tosylate	Unasyn	1987	ARMC 23	343	ND
tazobactam sodium	Tazocillin	1992	ARMC 28	336	ND
telithromycin	Ketek	2001	DNP 15	35	ND
temocillin disodium	Temopen	1984	ARMC 20	323	ND
tigecycline	Tygacil	2005	DNP 19	42	ND

Table 2. Continued

generic name	trade name	year introduced	reference	page	source
balafloxacin	Q-Roxin	2002	ARMC 38	351	S
ciprofloxacin	Ciprobay	1986	ARMC 22	318	S
enoxacin	Flumark	1986	ARMC 22	320	S
fleroxacin	Quinodis	1992	ARMC 28	331	S
gatilfloxacin	Tequin	1999	ARMC 35	340	S
gemifloxacin mesilate	Factive	2003	ARMC 40	458	S
grepafloxacin	Vaxor	1997	DNP 11	23	S
levofloxacin	Floxacin	1993	ARMC 29	340	S
linezolid	Zyvox	2000	DNP 14	21	S
lomefloxacin	Uniquin	1989	ARMC 25	315	S
moxifloxacin HCl	Avelox	1999	ARMC 35	343	S
nadifloxacin	Acuatim	1993	ARMC 29	340	S
norfloxacin	Noroxin	1983	ARMC 19	322	S
ofloxacin	Tarivid	1985	ARMC 21	331	S
pazufloxacin	Pasil	2002	ARMC 38	364	S
pefloxacin mesylate	Perflacine	1985	ARMC 21	331	S
prulifloxacin	Sword	2002	ARMC 38	366	S
rufloxacin hydrochloride	Qari	1992	ARMC 28	335	S
sparfloxacin	Spara	1993	ARMC 29	345	S
taurolidine	Taurolin	1988	I 107771		S
temafloxacin hydrochloride	Temac	1991	ARMC 27	334	S
tosufloxacin	Ozex	1990	ARMC 26	310	S
trovafloxacin mesylate	Trovan	1998	ARMC 34	332	S
brodimoprin	Hyprim	1993	ARMC 29	333	S*/NM
ACWY meningoccal PS vaccine	Mencevax	1981	I 420128		V
MCV-4	Menactra	2005	DNP 19	43	V
h influenzae b vaccine	Hibtitek	1989	DNP 03	24	V
h influenzae b vaccine	Prohibit	1989	DNP 03	24	V
meningitis b vaccine	MeNZB	2004	DNP 18	29	V
meningococcal vaccine	NeisVac-C	2000	DNP 14	22	V
meningococcal vaccine	Menjugate	2000	DNP 14	22	V
meningococcal vaccine	Menigetec	1999	DNP 14	22	V
oral cholera vaccine	Orochol	1994	DNP 08	30	V
pneumococcal vaccine	Prevnar	2000	DNP 14	22	V
vi polysaccharide typhoid vaccine	Typherix	1998	DNP 12	35	V

Table 3. Antifungal Drugs from 01/1981 to 06/2006 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	reference	page	source
interferon gamma-n1	OGamma100	1996	DNP 10	13	B
anidulafungin	Eraxis	2006	I 194685		ND
caspofungin acetate	Cancidas	2001	DNP 15	36	ND
micafungin sodium	Fungard	2002	ARMC 38	360	ND
amorolfine hydrochloride	Loceryl	1991	ARMC 27	322	S
butoconazole	Femstat	1986	ARMC 22	318	S
ciclopirox olamine	Loprox	1982	I 070449		S
cloconazole HCI	Pilzcin	1986	ARMC 22	318	S
eberconazole	Ebernet	2005	DNP 19	42	S
fenticonazole nitrate	Lomexin	1987	ARMC 23	334	S
fluconazole	Diflucan	1988	ARMC 24	303	S
flutrimazole	Micetal	1995	ARMC 31	343	S
fosfluconazole	Prodif	2003	DNP 17	49	S
itraconazole	Sporanox	1988	ARMC 24	305	S
ketoconazole	Nizoral	1981	I 116505		S
lanoconazole	Astat	1994	ARMC 30	302	S
luliconazole	Lulicon	2005	DNP 19	42	S
naftifine HCI	Exoderil	1984	ARMC 20	321	S
neticonazole HCI	Atolant	1993	ARMC 29	341	S
oxiconazole nitrate	Oceral	1983	ARMC 19	322	S
posaconazole	Noxafil	2005	DNP 19	42	S
sertaconazole nitrate	Dermofix	1992	ARMC 28	336	S
sulconazole nitrate	Exelderm	1985	ARMC 21	332	S
terconazole	Gyno-Terazol	1983	ARMC 19	324	S
tioconazole	Trosyl	1983	ARMC 19	324	S
voriconazole	Vfend	2002	ARMC 38	370	S
butenafine hydrochloride	Mentax	1992	ARMC 28	327	S/NM
liranaftate	Zefnart	2000	DNP 14	21	S/NM
terbinafine hydrochloride	Lamisil	1991	ARMC 27	334	S/NM

Overview of Results. The data that we have analyzed in a variety of ways are presented as a series of bar graphs and pie charts and two major tables in order to establish the overall pictures and then are further subdivided into some major therapeutic areas using a tabular format. Except where noted, the time frame covered was 01/1981−06/2006:

- New Approved Drugs: With all source categories (Figure 1)
- New Approved Drugs: By source/year (Figure 2)

Table 4. Antiviral Drugs from 01/1981 to 06/2006 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	reference	page	source
immunoglobulin intravenous	Gammagard Liquid	2005	I 231564		B
interferon alfa	Alfaferone	1987	I 215443		B
interferon alfa-2b	Viraferon	1985	I 165805		B
interferon alfa-n3	Alferon N	1990	DNP 04	104	B
interferon alfacon-1	Infergen	1997	ARMC 33	336	B
interferon beta	Frone	1985	I 115091		B
palivizumab	Synagis	1998	DNP 12	33	B
peginterferon alfa-2a	Pegasys	2001	DNP 15	34	B
peginterferon alfa-2b	Pegintron	2000	DNP 14	18	B
resp syncytial virus IG	RespiGam	1996	DNP 10	11	B
thymalfasin	Zadaxin	1996	DNP 10	11	B
interferon alfa-n1	Wellferon	1986	I 125561		B
enfuvirtide	Fuzeon	2003	ARMC 39	350	ND
zanamivir	Relenza	1999	ARMC 35	352	ND
delavirdine mesylate	Rescriptor	1997	ARMC 33	331	S
efavirenz	Sustiva	1998	ARMC 34	321	S
foscarnet sodium	Foscavir	1989	ARMC 25	313	S
imiquimod	Aldara	1997	ARMC 33	335	S
nevirapine	Viramune	1996	ARMC 32	313	S
propagermanium	Serosion	1994	ARMC 30	308	S
rimantadine HCI	Roflual	1987	ARMC 23	342	S
oseltamivir	Tamiflu	1999	ARMC 35	346	S/NM
abacavir sulfate	Ziagen	1999	ARMC 35	333	S*
acyclovir	Zovirax	1981	I 091119		S*
adefovir dipivoxil	Hepsera	2002	ARMC 38	348	S*
cidofovir	Vistide	1996	ARMC 32	306	S*
didanosine	Videx	1991	ARMC 27	326	S*
emtricitabine	Emtriva	2003	ARMC 39	350	S*
entecavir	Baraclude	2005	DNP 19	39	S*
epervudine	Hevizos	1988	I 157373		S*
famciclovir	Famvir	1994	ARMC 30	300	S*
ganciclovir	Cymevene	1988	ARMC 24	303	S*
inosine pranobex	Imunovir	1981	I 277341		S*
lamivudine	Epivir	1995	ARMC 31	345	S*
penciclovir	Vectavir	1996	ARMC 32	314	S*
sorivudine	Usevir	1993	ARMC 29	345	S*
stavudine	Zerit	1994	ARMC 30	311	S*
tenofovir disoproxil fumarate	Viread	2001	DNP 15	37	S*
valaciclovir HCl	Valtrex	1995	ARMC 31	352	S*
valganciclovir	Valcyte	2001	DNP 15	36	S*
zalcitabine	Hivid	1992	ARMC 28	338	S*
zidovudine	Retrovir	1987	ARMC 23	345	S*
amprenavir	Agenerase	1999	ARMC 35	334	S*/NM
atazanavir	Reyataz	2003	ARMC 39	342	S*/NM
darunavir	Prezista	2006	I 310829		S*/NM
fomivirsen sodium	Vitravene	1998	ARMC 34	323	S*/NM
fosamprenevir	Lexiva	2003	ARMC 39	353	S*/NM
indinavir sulfate	Crixivan	1996	ARMC 32	310	S*/NM
lopinavir	Kaletra	2000	ARMC 36	310	S*/NM
neflinavir mesylate	Viracept	1997	ARMC 33	340	S*/NM
ritonavir	Norvir	1996	ARMC 32	317	S*/NM
saquinavir mesylate	Invirase	1995	ARMC 31	349	S*/NM
tipranavir	Aptivus	2005	DNP 19	42	S*/NM
(no generic name)	VariZIG	2005	I 230590		V
MR vaccine	Mearubik	2005	DNP 19	44	V
anti-Hep B immunoglobulin	HepaGam B	2006	I 308662		V
attenuated chicken pox vaccine	Merieux Varicella Vaccine	1993	DNP 07	31	V
hepatitis A and B vaccine	Ambirix	2003	I 334416		V
hepatitis B vaccine	Fendrix	2005	DNP 19	43	V
hepatitis a vaccine	Havrix	1992	DNP 06	99	V
hepatitis a vaccine	Aimmugen	1995	DNP 09	23	V
hepatitis a vaccine	Vaqta	1996	DNP 10	11	V
hepatitis b vaccine	Bio-Hep B	2000	DNP 14	22	V
hepatitis b vaccine	Hepacure	2000	DNP 14	22	V
hepatitis b vaccine	Biken-HB	1993	DNP 07	31	V
hepatitis b vaccine	Meinyu	1997	DNP 11	24	V
hepatitis b vaccine	Engerix B	1987	I 137797		V
inact hepatitis a vaccine	Avaxim	1996	DNP 10	12	V
influenza vaccine	Invivac	2004	I 391186		V
influenza virus (live)	FluMist	2003	ARMC 39	353	V
rotavirus vaccine	Rota-Shield	1998	DNP 12	35	V
rotavirus vaccine	Rotarix	2005	DNP 18	29	V
rotavirus vaccine	Rotateq	2006	I 313952		V
rubella vaccine	Ervevax	1985	I 115078		V
varicella virus vaccine	Varivax	1995	DNP 09	25	V
zoster vaccine live	Xostavax	2006	I 330188		V
(no generic name)	Bilive	2005	DNP 19	43	V

Table 5. Antiparasitic Drugs from 01/1981 to 06/2006 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	reference	page	source
artemisinin	Artemisin	1987	ARMC 23	327	N
ivermectin	Mectizan	1987	ARMC 23	336	N
arteether	Artemotil	2000	DNP 14	22	ND
artemether	Artemetheri	1987	I 090712		ND
artenusate	Arinate	1987	I 091299		ND
eflornithine HCl	Ornidyl	1990	DNP 04	104	ND
mefloquine HCI	Fansimef	1985	ARMC 21	329	ND
albendazole	Eskazole	1982	I 129625		S
halofantrine	Halfan	1988	ARMC 24	304	S
lumefantrine	no trade name	1987	I 269095		S
quinfamide	Amenox	1984	ARMC 20	322	S
atovaquone	Mepron	1992	ARMC 28	326	S*
bulaquine/chloroquine	Aablaquin	2000	DNP 14	22	S*
trichomonas vaccine	Gynatren	1986	I 125543		V

Table 6. All Antiinfective (Antibacterial, Fungal, Parasitic, and Viral) Drugs ($N = 230$)

indication	total	B	N	ND	S	S/NM	S*	S*/NM	V
antibacterial	109		10	64	23			1	11
antifungal	29	1		3	22	3			
antiparasitic	14		2	5	4		2		1
antiviral	78	12		2	7	1	20	12	25
total	230	13	12	74	56	4	22	12	37
percentage	100.0	5.7	5.2	32.3	24.5	2.2	9.6	4.8	15.7

Table 7. Small Molecule Antiinfective (Antibacterial, Fungal, Parasitic, and Viral) Drugs ($N = 180$)

indication	total	N	ND	S	S/NM	S*	S*/NM
antibacterial	98	10	64	23			1
antifungal	29		3	22	3		
antiparasitic	13	2	5	4		2	
antiviral	41		2	7	1	20	12
total	180	12	74	56	4	22	11
percentage	100.0	6.7	41.1	31.1	2.8	12.2	6.1

- Sources of all NCEs: Where four or more drugs were approved per medical indication (Table 1)
- Sources of Small Molecule NCEs: All subdivisions (Figure 3)
- Sources of Small Molecule NCEs: By source/year (Figure 4)
- Antibacterial Drugs: Generic and trade names, year, reference, and source (Table 2)
- Antifungal Drugs: Generic and trade names, year, reference, and source (Table 3)
- Antiviral Drugs: Generic and trade names, year, reference, and source (Table 4)
- Antiparasitic Drugs: Generic and trade names, year, reference, and source (Table 5)
- Antiinfective Drugs: All molecules, source, and numbers (Table 6)
- Antiinfective Drugs: Small molecules, source, and numbers (Table 7)
- Anticancer Drugs: Generic and trade names, year, reference, and source (Table 8)
- All Anticancer Drugs: Generic names, reference, and source (Figures 5−7; and (1940s−06/2006) Table 9)
- Antidiabetic Drugs: Generic and trade names, year, reference, and source (Table 10)

The extensive data sets shown in the figures and tables referred to above highlight the continuing role that natural products and structures derived from or related to natural products from all sources have played and continue to play in the development of the current therapeutic armamentarium of the physician. Inspection of the data shows this continued important role for natural products in spite of the current low level of natural products-based drug discovery programs in major pharmaceutical houses.

Inspection of the rate of NCE approvals as shown in Figure 2 demonstrates that the natural products field is still producing or is involved in ~50% of all small molecules in the years 2000−2006 and that a significant number of NCEs are biologicals or vaccines (83 of 264, or 31.4%). This is so in spite of many years of work by the pharmaceutical industry devoted to high-throughput screening of predominately combinatorial chemistry products and that the time period chosen should have provided a sufficient time span for combinatorial chemistry work from the late 1980s onward to have produced approved NCEs.

Overall, of the 1184 NCEs covering all diseases/countries/sources in the years 01/1981−06/2006, and using the "NM" classifications introduced in our 2003 review,[1,2] 30% were synthetic in origin, thus demonstrating the influence of "other than formal synthetics" on drug discovery and approval (Figure 1).

Inspection of Table 1 demonstrates that, overall, the major disease areas that have been investigated (in terms of numbers of drugs approved) in the pharmaceutical industry continue to be infectious diseases (microbial, parasitic, and viral), cancer, antihypertensives, and antiinflammatory indications, all with over 50 approved drug therapies. It should be noted, however, that numbers of approved drugs/disease do not correlate with the "value" as measured by sales, since the best selling drug of all is atorvastin, a hypocholesterolemic descended directly from a natural product, which sold over $11 billion in 2004 and is at or above this level even today.

The major category by far is that of antiinfectives including antiviral vaccines, with 230 (22.8%) of the total (1010 for indications ≥ 4) falling into this one major human disease area. On further analyses (Tables 6 and 7), the influence of biologicals and vaccines in this disease complex is such that only a little over 30% are synthetic in origin. If one considers only small molecules (reducing the total by 50 to 180; Table 10), then the synthetic figure goes up to 31.1%, marginally greater than in our previous report.[2] As reported previously,[1,2] these synthetic drugs actually tend to be of two basic chemotypes, the azole-based antifungals and the quinolone-based antibacterials.

Four small molecule drugs were approved in the antibacterial area from 01/2003 to 06/2006. These included daptomycin (N, **5**) from Cubist, a lipopeptide whose biosynthetic cluster has been successfully cloned and expressed by investigators associated with Cubist.[71] Wyeth had their modified tetracycline derivative, tigecycline, approved (ND, **6**), a drug designed to overcome the *tet* resistance pump in pathogenic bacteria, and another carbapenem (ND) and a quinolone (S) were also approved in this time frame. In the antifungal area, of the five drugs approved, four were azoles (S) and the echinocandin derivative, anidulofungin (ND), was approved for use in the U.S. in early 2006. In the antiviral area, seven drugs were approved for HIV treatment (1 ND, 1 S*, 5 S*/NM). It is interesting that the one ND, enfuvirtide, though listed in most literature as a synthetic, is actually the "end-capped" 36-

Table 8. Anticancer Drugs from 01/1981−06/2006 Organized Alphabetically by Generic Name within Source

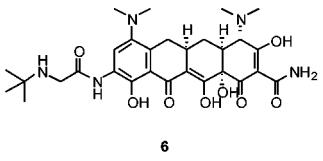
generic name	trade name	year introduced	reference	page	source
H-101	none given[a]	2005	DNP 19	46	B
alemtuzumab	Campath	2001	DNP 15	38	B
bevacizumab	Avastin	2004	ARMC 40	450	B
celmoleukin	Celeuk	1992	DNP 06	102	B
cetuximab	Erbitux	2003	ARMC 39	346	B
denileukin diftitox	Ontak	1999	ARMC 35	338	B
ibritumomab	Zevalin	2002	ARMC 38	359	B
interferon alfa2a	Roferon-A	1986	I 204503		B
interferon, gamma-1a	Biogamma	1992	ARMC 28	332	B
interleukin-2	Proleukin	1989	ARMC 25	314	B
mobenakin	Octin	1999	ARMC 35	345	B
pegaspargase	Oncaspar	1994	ARMC 30	306	B
rituximab	Rituxan	1997	DNP 11	25	B
tasonermin	Beromun	1999	ARMC 35	349	B
teceleukin	Imumace	1992	DNP 06	102	B
tositumomab	Bexxar	2003	ARMC 39	364	B
trastuzumab	Herceptin	1998	DNP 12	35	B
aclarubicin	Aclacin	1981	I 090013		N
angiotensin II	Delivert	1994	ARMC 30	296	N
arglabin	none given[a]	1999	ARMC 35	335	N
masoprocol	Actinex	1992	ARMC 28	333	N
paclitaxel	Taxol	1993	ARMC 29	342	N
paclitaxel nanoparticles	Abraxane	2005	DNP 19	45	N
pentostatin	Nipent	1992	ARMC 28	334	N
peplomycin	Pepleo	1981	I 090889		N
solamargines	Curaderm	1989	DNP 03	25	N
alitretinoin	Panretin	1999	ARMC 35	333	ND
amrubicin HCl	Calsed	2002	ARMC 38	349	ND
belotecan hydrochloride	Camtobell	2004	ARMC 40	449	ND
cladribine	Leustatin	1993	ARMC 29	335	ND
cytarabine ocfosfate	Starsaid	1993	ARMC 29	335	ND
docetaxel	Taxotere	1995	ARMC 31	341	ND
elliptinium acetate	Celiptium	1983	I 091123		ND
epirubicin HCI	Farmorubicin	1984	ARMC 20	318	ND
etoposide phosphate[b]	Etopophos	1996	DNP 10	13	ND
exemestane	Aromasin	1999	DNP 13	46	ND
formestane	Lentaron	1993	ARMC 29	337	ND
fulvestrant	Faslodex	2002	ARMC 38	357	ND
gemtuzumab ozogamicin	Mylotarg	2000	DNP 14	23	ND
hexyl aminolevulinate	Hexvix	2004	I 300211		ND
idarubicin hydrochloride	Zavedos	1990	ARMC 26	303	ND
irinotecan hydrochloride	Campto	1994	ARMC 30	301	ND
miltefosine	Miltex	1993	ARMC 29	340	ND
pirarubicin	Pinorubicin	1988	ARMC 24	309	ND
talaporfin sodium	Laserphyrin	2004	ARMC 40	469	ND
topotecan HCl	Hycamptin	1996	ARMC 32	320	ND
triptorelin	Decapeptyl	1986	I 090485		ND
valrubicin	Valstar	1999	ARMC 35	350	ND
vapreotide acetate	Docrised	2004	I 135014		ND
vinorelbine	Navelbine	1989	ARMC 25	320	ND
zinostatin stimalamer	Smancs	1994	ARMC 30	313	ND
aminoglutethimide	Cytadren	1981	I 070408		S
amsacrine	Amsakrin	1987	ARMC 23	327	S
arsenic trioxide	Trisenox	2000	DNP 14	23	S
bisantrene hydrochloride	Zantrene	1990	ARMC 26	300	S
carboplatin	Paraplatin	1986	ARMC 22	318	S
flutamide	Drogenil	1983	ARMC 19	318	S
fotemustine	Muphoran	1989	ARMC 25	313	S
heptaplatin/SK-2053R	Sunpla	1999	ARMC 35	348	S
lobaplatin	Lobaplatin	1998	DNP 12	35	S
lonidamine	Doridamina	1987	ARMC 23	337	S
nedaplatin	Aqupla	1995	ARMC 31	347	S
nilutamide	Anadron	1987	ARMC 23	338	S
oxaliplatin	Eloxatin	1996	ARMC 32	313	S
porfimer sodium	Photofrin	1993	ARMC 29	343	S
ranimustine	Cymerine	1987	ARMC 23	341	S
sobuzoxane	Parazolin	1994	ARMC 30	310	S
sorafenib	Nexavar	2005	DNP 19	45	S
anastrozole	Arimidex	1995	ARMC 31	338	S/NM
bicalutamide	Casodex	1995	ARMC 31	338	S/NM
bortezomib	Velcade	2003	ARMC 39	345	S/NM
camostat mesylate	Foipan	1985	ARMC 21	325	S/NM
erlotinib hydrochloride	Tarceva	2004	ARMC 40	454	S/NM
fadrozole HCl	Afema	1995	ARMC 31	342	S/NM
gefitinib	Iressa	2002	ARMC 38	358	S/NM
imatinib mesilate	Gleevec	2001	DNP 15	38	S/NM
letrazole	Femara	1996	ARMC 32	311	S/NM

Table 8. Continued

generic name	trade name	year introduced	reference	page	source
sunitinib malate	Sutent	2006	I 309144		S/NM
temoporfin	Foscan	2002	I 158118		S/NM
toremifene	Fareston	1989	ARMC 25	319	S/NM
zoledronic acid	Zometa	2000	DNP 14	24	S
azacytidine	Vidaza	2004	ARMC 40	447	S*
capecitabine	Xeloda	1998	ARMC 34	319	S*
carmofur	Mifurol	1981	I 091100		S*
clofarabine	Clolar	2005	DNP 19	44	S*
decitabine	Dacogen	2006	I 125366		S*
doxifluridine	Furtulon	1987	ARMC 23	332	S*
enocitabine	Sunrabin	1983	ARMC 19	318	S*
fludarabine phosphate	Fludara	1991	ARMC 27	327	S*
gemcitabine HCl	Gemzar	1995	ARMC 31	344	S*
mitoxantrone HCI	Novantrone	1984	ARMC 20	321	S*
nelarabine	Arranon	2005	DNP 19	45	S*
abarelix	Plenaxis	2004	ARMC 40	446	S*/NM
bexarotene	Targretine	2000	DNP 14	23	S*/NM
pemetrexed disodium	Alimta	2004	ARMC 40	463	S*/NM
raltitrexed	Tomudex	1996	ARMC 32	315	S*/NM
tamibarotene	Amnoid	2005	DNP 19	45	S*/NM
temozolomide	Temodal	1999	ARMC 35	350	S*/NM
bcg live	TheraCys	1990	DNP 04	104	V
melanoma theraccine	Melacine	2001	DNP 15	38	V

[a] No trade name given in the original report nor in the Prous Integrity database. [b] A prodrug of etoposide.

residue peptide that corresponds to residues 643−678 of the HIV-1 transmembrane protein gp41 and blocks viral fusion with the cell.[72] In addition to this novel mechanism, four new HIV protease inhibitors were approved; all were peptidomimetics imitating the peptide substrate, and the latest one, darunavir (**7**), actually has the hydroxyethyl isostere that was first identified in the microbial aspartic protease inhibitor pepstatin and incorporated in the base structure of crixivan (see discussion by Yang et al.[73]).



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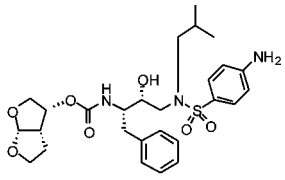

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It should be noted that the percentages used in the following overall analyses do not always agree with those in the later tables, as all sources, which include B and V categorized drugs, and all indications are included in the percentage figures used in the analyses. Much fuller details are given in the Supporting Information in the form of an Excel XP spreadsheet.

As we reported in our earlier analyses,[1,2] there are still significant therapeutic classes where the available drugs are totally synthetic at the present time. These include antihistamines, diuretics, and hypnotics for indications with four or more approved drugs (cf. Table 1). There are a substantial number of indications where there are three or less drugs that are also totally synthetic. Because of our introduction of the "NM" subcategory, indications such as antidepressants and cardiotonics now have substantial numbers that, although formally "S", now fall into the "S/NM" subcategory.

From inspection of Tables 1−4 and 8 and the Excel XP spreadsheet, the following points can be made in addition to the digest on antiinfectives given in Tables 6 and 7. In the antibacterial area (Table 2), as found previously, the vast majority of the 98 small molecule NCEs are N (10; 10.2%), ND (64; 65.3%), or S*/NM (1; 1%), amounting to 75 in total, or 76.5% of the whole, with the remainder (S) being predominately quinolones. In the antifungal area (Table 3), the roles of the small molecules (n = 28) are reversed, with the great majority being S (22; 78.6%) and S/NM (3; 10.7%), with the remainder being ND (3; 10.7%).

In the antiviral area (Table 4), the situation is somewhat different, with a large number of vaccines (n = 25) now added to this category. If we consider only small molecules, the anti-HIV drugs being approved are based mainly on nucleoside structures (S*) or on peptidomimetics (S* and S/NM), and drugs against other viral diseases also fall into these categories. Thus, one can see that of the 42 small molecule approved antiviral agents, the relevant figures are ND (2; 4.8%), S* and S*/NM categories (32; 76.2%), with the remainder falling into either S (7; 16.7%) or S/NM (1; 2.4%).

We have also identified the antiparasitic drugs that have been approved over the years (Table 5) and point out that of the 14 small molecule drugs, only four are synthetic (28.5%) and of the rest, three are artemisinin derivatives. What is of interest with this base structure is that, in addition to their known antimalarial activities, compounds based on this structure are demonstrating activity as antitumor agents.[74]

With anticancer drugs (Table 8), where in the time frame covered (01/1981−06/2006) there were 100 NCEs *in toto*, the number of nonbiologicals was 81 (81%). These small molecules could be divided as follows (using 81 = 100%) into N (9; 11.1%), ND (25; 30.9%), S (18; 22.2%), S/NM (12; 14.8%), S* (11; 13.6%), and S*/NM (6; 7.4%). Thus, using our criteria, only 22.2% of the total number of anticancer drugs were classifiable into the S (synthetic) category. Expressed as a proportion of the nonbiologicals/vaccines, then 63 of 81 (77.8%) were either natural products per se or were based thereon, or mimicked natural products in one form or another.

In this current review, we have continued as in our previous contribution (2003)[2] to reassess the influence of natural products and their mimics as leads to anticancer drugs. By using data from the FDA listings of antitumor drugs, coupled with our previous data sources and with help from Japanese colleagues, we have been able to identify the years in which all but 18 of the 175 drugs we have listed in Table 9 were approved. We have identified these other 18 agents by inspection of three time-relevant textbooks on antitumor treatment,[51,75,76] and these were added to the overall listings using the lead authors' names as the source citation.

Inspection of Figures 5−7 and Table 9 shows that, over the whole category of anticancer drugs effectively available to the West and Japan, the 175 available agents can be categorized as follows: B (18; 10%), N (25; 14%), ND (48; 28%), S (42; 24%), S/NM (14; 8%), S* (20; 11%), S*/NM (6; 4%), and V (2; 1%). If one removes the biologicals and vaccines, reducing the overall number to 155 (100%), the number of naturally inspired agents (i.e., N, ND, S/NM, S*, S*/NM) is 113 (72.9%). It should be noted that these 155 agents do not include some of the earlier drugs that were really immuno-

Table 9. All Anticancer Drugs (1940s−07/2006)[a] Organized Alphabetically by Generic Name within Source

generic name	year introduced	reference	page	source
H-101	2005	DNP 19	46	B
aldesleukin	1992	ARMC 25	314	B
alemtuzumab	2001	DNP 15	38	B
bevacizumab	2004	ARMC 40	450	B
celmoleukin	1992	DNP 06	102	B
cetuximab	2003	ARMC 39	346	B
denileukin diftitox	1999	ARMC 35	338	B
interferon alfa2a	1986	I 204503		B
interferon alfa2b	1986	I 165805		B
interferon, gamma-1a	1992	ARMC 28	332	B
interleukin-2	1989	ARMC 25	314	B
mobenakin	1999	ARMC 35	345	B
pegaspargase	1994	ARMC 30	306	B
rituximab	1997	DNP 11	25	B
tasonermin	1999	ARMC 35	349	B
teceleukin	1992	DNP 06	102	B
tositumomab	2003	ARMC 39	364	B
trastuzumab	1998	DNP 12	35	B
aclarubicin	1981	I 090013		N
actinomycin D	1964	FDA		N
angiotensin II	1994	ARMC 30	296	N
arglabin	1999	ARMC 35	335	N
asparaginase	1969	FDA		N
bleomycin	1966	FDA		N
carzinophilin	1954	Japan Antibiotics		N
chromomycin A3	1961	Japan Antibiotics		N
daunomycin	1967	FDA		N
doxorubicin	1966	FDA		N
leucovorin	1950	FDA		N
masoprocol	1992	ARMC 28	333	N
mithramycin	1961	FDA		N
mitomycin C	1956	FDA		N
neocarzinostatin	1976	Japan Antibiotics		N
paclitaxel	1993	ARMC 29	342	N
palictaxel nanoparticles	2005	DNP 19	45	N
pentostatin	1992	ARMC 28	334	N
peplomycin	1981	I 090889		N
sarkomycin	1954	FDA		N
solamargine (aka BEC)	1987	DNP 03	25	N
streptozocin	pre-1977			N
testosterone	pre-1970			N
vinblastine	1965	FDA		N
vincristine	1963	FDA		N
alitretinoin	1999	ARMC 35	333	ND
amrubicin HCl	2002	ARMC 38	349	ND
belotecan hydrocholoride	2004	ARMC 40	449	ND
calusterone	1973	FDA		ND
cladribine	1993	ARMC 29	335	ND
cytarabine ocfosfate	1993	ARMC 29	335	ND
dexamethasone	1958	FDA		ND
docetaxel	1995	ARMC 31	341	ND
dromostanolone	1961	FDA		ND
elliptinium acetate	1983	I 091123		ND
epirubicin HCI	1984	ARMC 20	318	ND
estramustine	1980	FDA		ND
ethinyl estradiol	pre-1970			ND
etoposide	1980	FDA		ND
exemestane	1999	DNP 13	46	ND
fluoxymesterone	pre-1970			ND
formestane	1993	ARMC 29	337	ND
fosfestrol	pre-1977			ND
fulvestrant	2002	ARMC 38	357	ND
gemtuzumab ozogamicin	2000	DNP 14	23	ND
goserelin acetate	1987	ARMC 23	336	ND
hexyl aminolevulinate	2004	I 300211		ND
histrelin	2004	I 109865		ND
hydroxyprogesterone	pre-1970			ND
idarubicin hydrochloride	1990	ARMC 26	303	ND
irinotecan hydrochloride	1994	ARMC 30	301	ND
leuprolide	1984	ARMC 20	319	ND
medroxyprogesterone acetate	1958	FDA		ND
megesterol acetate	1971	FDA		ND
methylprednisolone	1955	FDA		ND
methyltestosterone	1974	FDA		ND
miltefosine	1993	ARMC 29	340	ND
mitobronitol	1979	FDA		ND
nadrolone phenylpropionate	1959	FDA		ND

Table 9. Continued

generic name	year introduced	reference	page	source
norethindrone acetate	pre-1977			ND
pirarubicin	1988	ARMC 24	309	ND
prednisolone	pre-1977			ND
prednisone	pre-1970			ND
teniposide	1967	FDA		ND
testolactone	1969	FDA		ND
topotecan HCl	1996	ARMC 32	320	ND
triamcinolone	1958	FDA		ND
triptorelin	1986	I 090485		ND
valrubicin	1999	ARMC 35	350	ND
vapreotide acetate	2003	I 135014		ND
vindesine	1979	FDA		ND
vinorelbine	1989	ARMC 25	320	ND
zinostatin stimalamer	1994	ARMC 30	313	ND
amsacrine	1987	ARMC 23	327	S
arsenic trioxide	2000	DNP 14	23	S
bisantrene hydrochloride	1990	ARMC 26	300	S
busulfan	1954	FDA		S
carboplatin	1986	ARMC 22	318	S
carmustine (BCNU)	1977	FDA		S
chlorambucil	1956	FDA		S
chlortrianisene	pre-1981	BOYD		S
cis-diamminedichloroplatinum	1979	FDA		S
cyclophosphamide	1957	FDA		S
dacarbazine	1975	FDA		S
diethylstilbestrol	pre-1970			S
flutamide	1983	ARMC 19	318	S
fotemustine	1989	ARMC 25	313	S
heptaplatin/SK-2053R	1999	ARMC 35	348	S
hexamethylmelamine	1979	FDA		S
hydroxyurea	1968	FDA		S
ifosfamide	1976	FDA		S
lenalidomide	2005	DNP 19	45	S
levamisole	pre-1981	Boyd		S
lobaplatin	1998	DNP 12	35	S
lomustine (CCNU)	1976	FDA		S
lonidamine	1987	ARMC 23	337	S
mechlorethanamine	1958	FDA		S
melphalan	1961	FDA		S
mitotane	1970	FDA		S
nedaplatin	1995	ARMC 31	347	S
nilutamide	1987	ARMC 23	338	S
nimustine hydrochloride	pre-1981	Boyd		S
oxaliplatin	1996	ARMC 32	313	S
pamidronate	1987	ARMC 23	326	S
pipobroman	1966	FDA		S
porfimer sodium	1993	ARMC 29	343	S
procarbazine	1969	FDA		S
ranimustine	1987	ARMC 23	341	S
razoxane	pre-1977			S
semustine (MCCNU)	pre-1977			S
sobuzoxane	1994	ARMC 30	310	S
sorafenib mesylate	2005	DNP 19	45	S
thiotepa	1959	FDA		S
triethylenemelamine	pre-1981	Boyd		S
zoledronic acid	2000	DNP 14	24	S
anastrozole	1995	ARMC 31	338	S/NM
bicalutamide	1995	ARMC 31	338	S/NM
bortezomib	2003	ARMC 39	345	S/NM
camostat mesylate	1985	ARMC 21	325	S/NM
dasatinib[a]	2006	I 365055		S/NM
erlotinib hydrochloride	2004	ARMC 40	454	S/NM
fadrozole HCl	1995	ARMC 31	342	S/NM
gefitinib	2002	ARMC 38	358	S/NM
imatinib mesilate	2001	DNP 15	38	S/NM
letrozole	1996	ARMC 32	311	S/NM
nafoxidine	pre-1977			S/NM
sunitinib maleate	2006	I 309144		S/NM
tamoxifen	1973	FDA		S/NM
toremifene	1989	ARMC 25 319		S/NM
aminoglutethimide	1981	FDA		S*
azacytidine	pre-1977			S*
capecitabine	1998	ARMC 34	319	S*
carmofur	1981	FDA		S*
clofarabine	2005	DNP 19	44	S*

Table 9. Continued

generic name	year introduced	reference	page	source
cytosine arabinoside	1969	FDA		S*
decitabine	2006	I 125366		S*
doxifluridine	1987	ARMC 23	332	S*
enocitabine	1983	ARMC 19	318	S*
floxuridine	1971	FDA		S*
fludarabine phosphate	1991	ARMC 27	327	S*
fluorouracil	1962	FDA		S*
ftorafur	1972	FDA		S*
gemcitabine HCl	1995	ARMC 31	344	S*
mercaptopurine	1953	FDA		S*
methotrexate	1954	FDA		S*
mitoxantrone HCI	1984	ARMC 20	321	S*
nelarabine	2005	DNP 19	45	S*
thioguanine	1966	FDA		S*
uracil mustard	1966	FDA		S*
abarelix	2004	ARMC 40	446	S*/NM
bexarotene	2000	DNP 14	23	S*/NM
pemetrexed	2004	ARMC 40	463	S*/NM
raltitrexed	1996	ARMC 32	315	S*/NM
tamibarotene	2005	DNP 19	45	S*/NM
temozolomide	1999	ARMC 35	350	S*/NM
bcg live	1990	DNP 04	104	V
melanoma theraccine	2001	DNP 15	38	V

[a] One extra drug added, approved June 28, 2006, launched July 3, 2006.

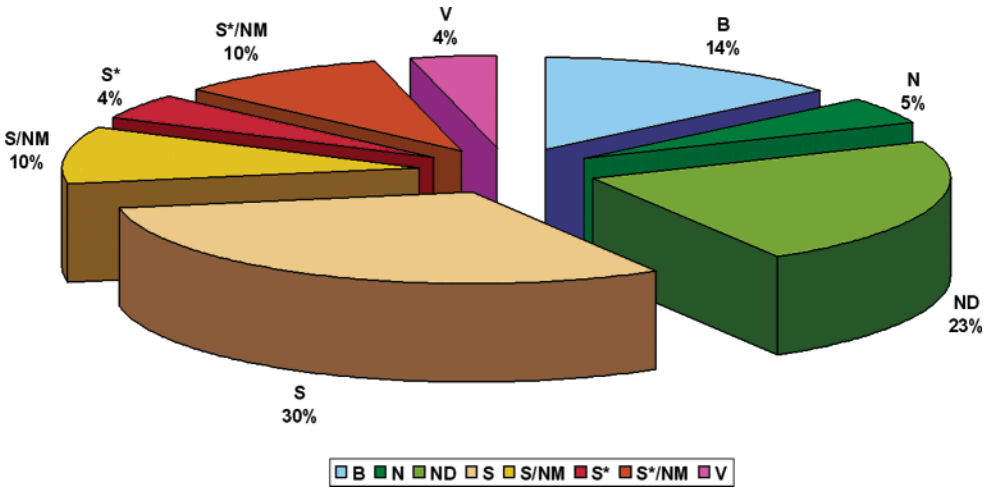

Figure 1. All new chemical entities, 01/1981−06/2006, by source (N = 1184).

or hematologic stimulants. Etoposide phosphate is not included in this count, as it is a prodrug of etoposide, though it was included in our last review as an approved NCE. We have however included paclitaxel nanoparticles, as this is not just a salt form but is a novel form of the agent ensuring much better water solubility.

In our earlier papers, the number of nonsynthetic antitumor agents was 62% for other than biologicals/vaccines, without an "NM" subcategory. The corresponding figure obtained by removing the NM subcategory in this analysis is 64%. Thus, the proportion has remained similar in spite of some reassignments of sources and the expansion of combinatorial chemistry techniques. As mentioned earlier, the first and only *de novo* combinatorial drug that we have been able to identify was approved by the FDA in 2005 under the generic name of sorafenib mesylate (**1**) for the treatment of advanced renal cancer.

A major general class of drugs that was not commented on in any detail in our earlier papers is the class that is directed toward the treatment of diabetes, both types I and II (Table 10; n = 32). These drugs include a significant number of biologics based upon varying modifications of insulin produced in general by biotechnological means (B, 18; 56.3%).[50] In addition to these well-known agents, the class also includes a very interesting compound (approved by the FDA in 2005) that is assigned to the ND class (extenatide or Byetta). This is the first in a new class of therapeutic agents known as incretin mimetics. The drug exhibits glucose-lowering activity similar to the naturally occurring incretin hormone glucagon-like peptide-1 (GLP-1), but is a 39-residue peptide based upon one of the peptide venoms of the Gila monster, *Heloderma suspectum*.[77]

Discussion

As alluded to in our previous review, the decline or leveling of the output of the R&D programs of the pharmaceutical companies has continued, with the number of drugs of all types dropping in 2003 to 35 launches, including 13 in the B/V categories, and reaching a nadir in 2004, when only 25 were launches and 6 of these fell into the B/V categories. There was a significant upswing in 2005 with 54 launches, but 20 of these were in the B/V categories, leaving 34 small molecules. In the first 6 months of 2006, of the 22 launches, 9 were B/V.

Although combinatorial chemistry continues to play a major role in the drug development process, as mentioned earlier, it is noteworthy that the trend toward the synthesis of complex natural product-like libraries has continued. As was eloquently stated by Danishefsky in 2002, "*a small collection of smart compounds may be more valuable than a much larger hodgepodge collection mindlessly assembled*".[78] Recently he and a coauthor restated this theme:[79]

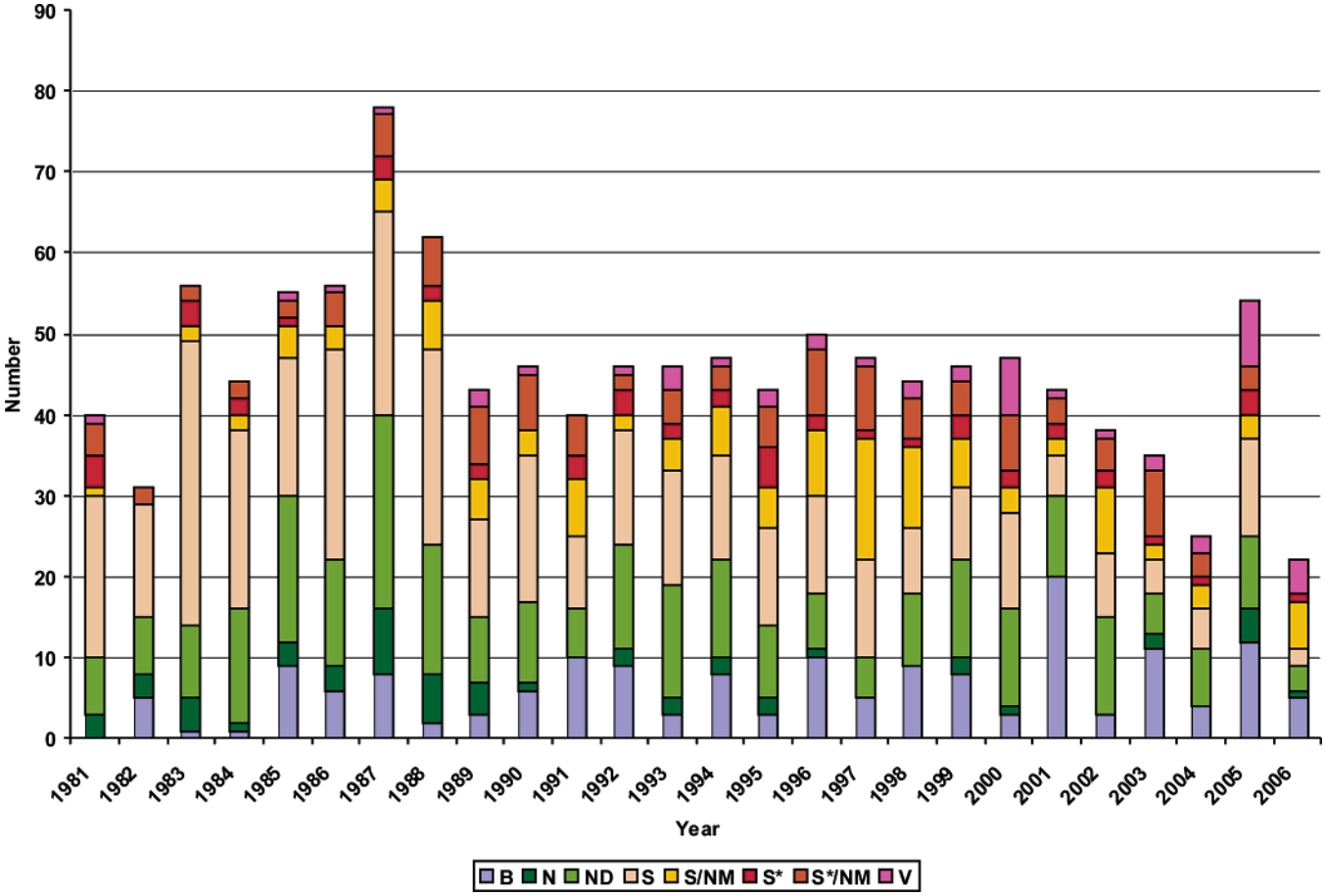

Figure 2. All new chemical entities organized by source/year ($N = 1184$).

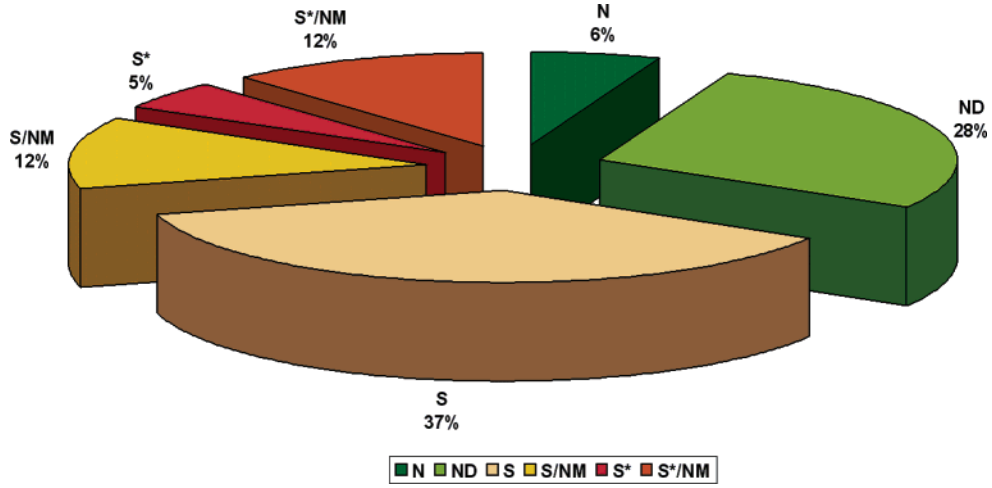

Figure 3. All small molecule new chemical entities, 01/1981−06/2006, by Source ($N = 974$).

In summary, we have presented several happy experiences in the course of our program directed toward bringing to bear nature's treasures of small molecule natural products on the momentous challenge of human neurodegenerative diseases. While biological results are now being accumulated for systematic disclosure, it is already clear that there is considerable potential in compounds obtained through plowing in the landscape of natural products. Particularly impressive are those compounds that are obtained through diverted total synthesis, i.e., through methodology, which was redirected from the original (and realized) goal of total synthesis, to encompass otherwise unavailable congeners. We are confident that the program will lead, minimally, to compounds that are deserving of serious preclinical follow-up. At the broader level, we note that this program will confirm once again (if further confirmation is, indeed, necessary) the extraordinary advantages of small molecule natural products as sources of agents, which interject themselves in a helpful way in various physiological processes.

We close with the hope and expectation that enterprising and hearty organic chemists will not pass up the unique head start that natural products provide in the quest for new agents and new directions in medicinal discovery. We would chance to predict that even as the currently fashionable "telephone directory" mode of research is subjected to much overdue scrutiny and performance-based assessment, organic chemists in concert with biologists and even clinicians will be enjoying as well as exploiting the rich troves provided by nature's small molecules.

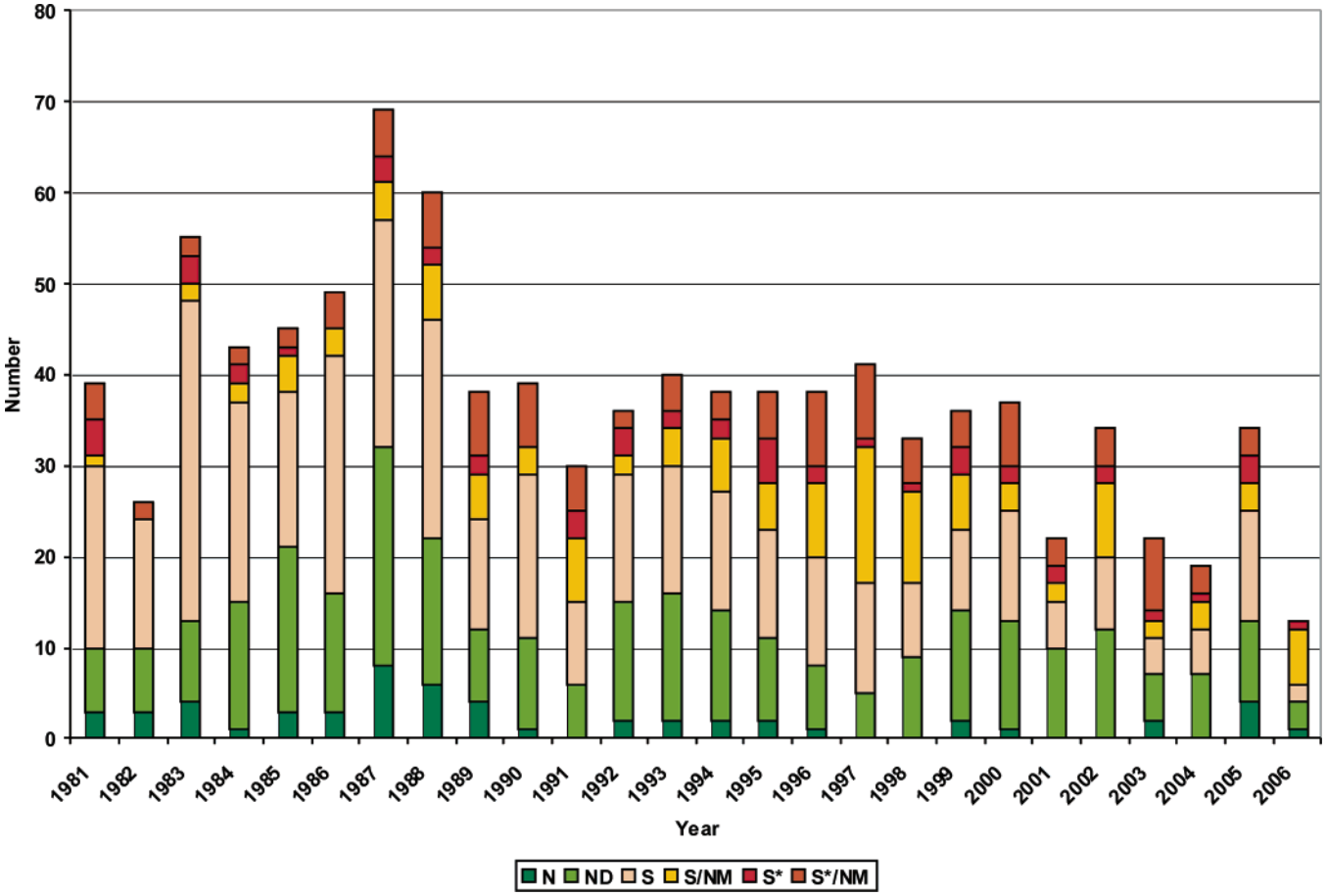

Figure 4. Small molecule new chemical entities organized by source/year ($N = 974$).

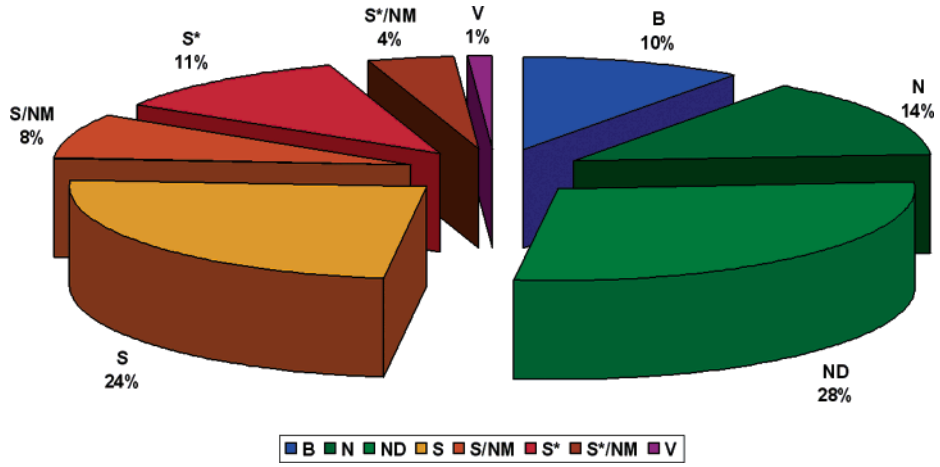

Figure 5. All available anticancer drugs, 1940s−06/2006, by source ($N = 175$).

A rapid analysis of the entities approved from 2003 to 2006 (the full data set is available as an Excel spreadsheet in the Supporting Information) indicated that there were significant numbers of antitumor, antibacterial, and antifungal agents approved as mentioned above. This time frame also saw two very important approvals, both of which were natural products. The first was the approval by the FDA, after a long series of trials and discussions, of the cone snail toxin known as Prialt, which is the first "direct from the sea" entity to become a licensed pharmaceutical.[80,81] Although one can argue (as we have on other occasions) that the discovery of the arabinose nucleosides by Bergmann in the 1950s was the driving force behind Ara-A, Ara-C, AZT, etc., this is the first direct transition from marine invertebrate to man. Also in the middle of 2006, the botanical preparation Hemoxin[82,83] was approved in Nigeria following demonstration of efficacy in clinical trials as a treatment for sickle cell anemia. This is a mix of plants that came from native healer information and thus can be classified as a "true ethnobotanical preparation".

In this paper, as we stated in 2003,[2] we have again demonstrated that natural products play a dominant role in the discovery of leads for the development of drugs for the treatment of human diseases. Some have argued (though not in press, only in personal conversations at various fora) that the introduction of categories such as S/NM and S*/NM is an overstatement of the role played by natural products in the drug discovery process. On the contrary, we would argue that these further serve to illustrate the inspiration provided by Nature to receptive organic chemists in devising ingenious syntheses of structural mimics to compete with Mother Nature's

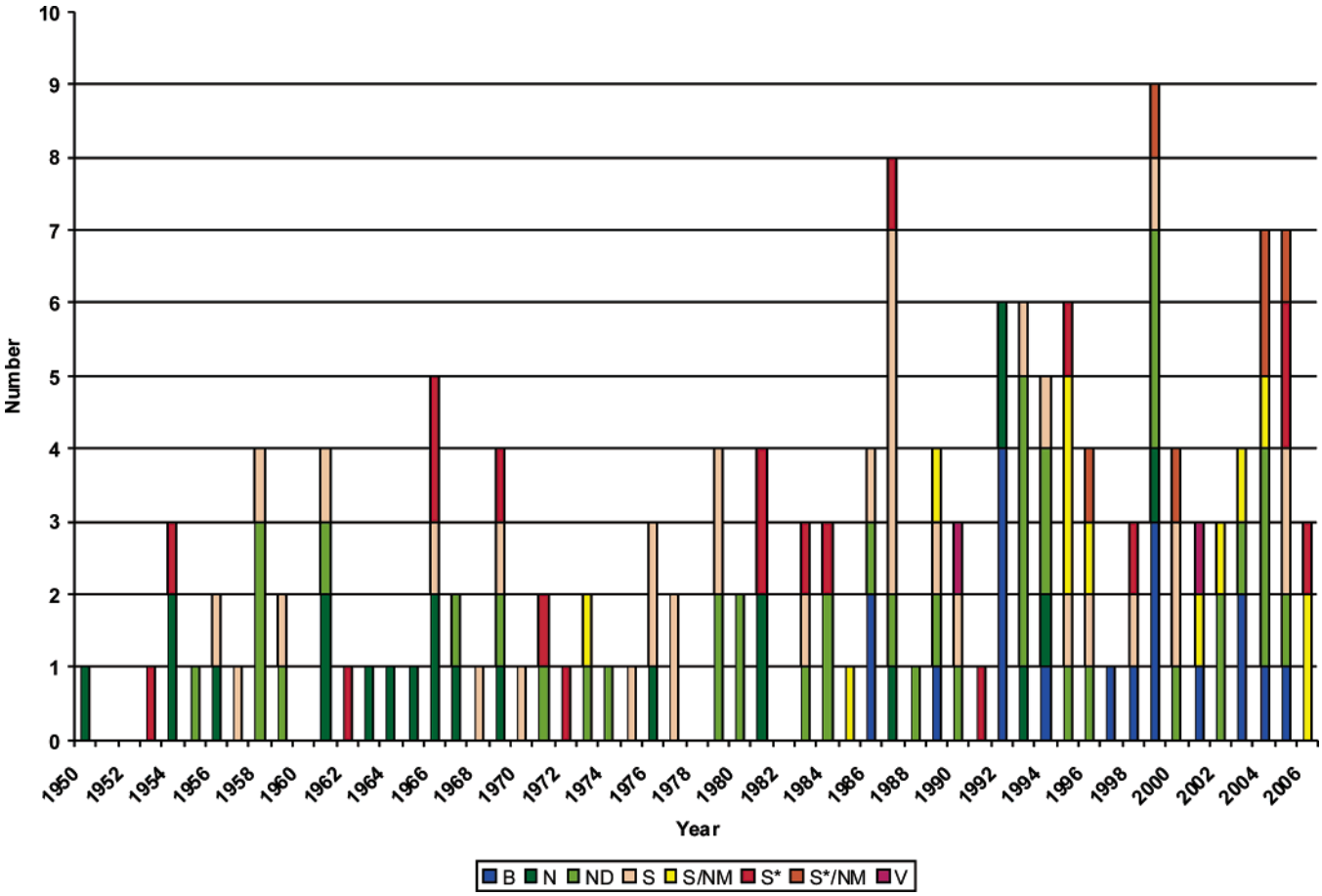

Figure 6. Approved anticancer agents, organized by source/year (known dates for 157).

Table 10. Antidiabetic Drugs from 01/1981 to 06/2006 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	reference	page	source
biphasic porcine insulin	Pork Mixtard 30	1982	I 303034		B
hu neutral insulin	Insuman	1992	I 255451		B
human insulin Zn suspension	Humulin L	1985	I 302828		B
human insulin zinc suspension	Humulin Zn	1985	I 091584		B
human neutral insulin	Novolin R	1991	I 182551		B
insulin aspart	NovoRapid	1999	DNP 13	41	B
insulin aspart/IA protamine	NovoMix 30	2001	DNP 15	34	B
insulin determir	Levemir	2004	DNP 18	27	B
insulin glargine	Lantus	2000	DNP 14	19	B
insulin glulisine	Apidra	2005	DNP 19	39	B
insulin lispro	Humalog	1996	ARMC 32	310	B
isophane insulin	Humulin N	1982	I 091583		B
mecasermin	Somazon	1994	DNP 08	28	B
oral insulin	Oral-lyn	2005	DNP 19	39	B
porcine isophane insulin	Pork Insulatard	1982	I 302757		B
porcine neutral insulin	Pork Actrapid	1998	I 302749		B
pulmonary insulin	Exubera	2005	I 229896		B
soluble insulin	Velosulin BR	1986	I 091581		B
voglibose	Basen	1994	ARMC 30	313	N
acarbose	Glucobay	1990	DNP 03	23	ND
extenatide	Byetta	2005	DNP 19	40	ND
miglitol	Diastabol	1998	ARMC 34	325	ND
triproamylin acetate	Normylin	2005	DNP 19	40	ND
glimepiride	Amaryl	1995	ARMC 31	344	S
mitiglinide calcium hydrate	Glufast	2004	ARMC 40	460	S
pioglitazone NCl	Actos	1999	ARMC 35	346	S
repaglinide	Prandin	1998	ARMC 34	329	S
epalrestat	Kinedak	1992	ARMC 28	330	S/NM
rosiglitazone maleate	Avandia	1999	ARMC 35	348	S/NM
tolrestat	Alredase	1989	ARMC 25	319	S/NM
troglitazone	Rezulin	1997	ARMC 33	344	S/NM
nateglinide	Starsis	1999	ARMC 35	344	S*

longstanding substrates. Even discounting these categories, the continuing and overwhelming contribution of natural products to the expansion of the chemotherapeutic armamentarium is clearly evident, and as we stated in our earlier papers, much of Nature's "treasure trove of small molecules" remains to be explored, particularly from the marine and microbial environments.

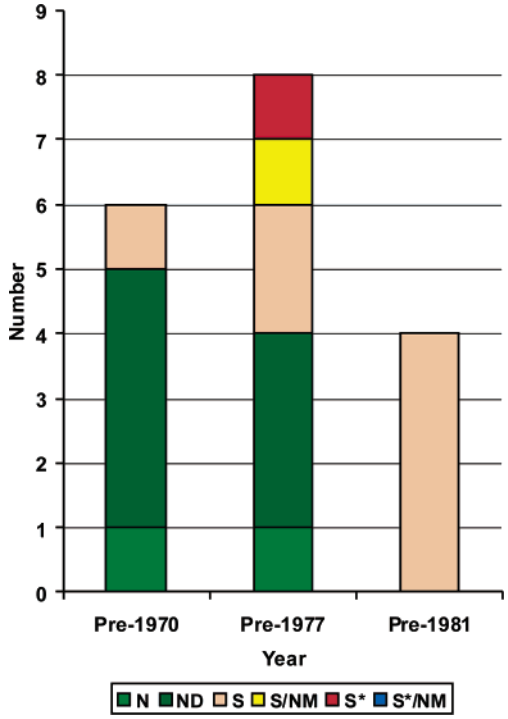

Figure 7. Approved anticancer agents, organized by source/year (unknown dates for 18).

From the perspective of microbes and their role(s) as sources of novel bioactive entities, the recent work that has been reported by a variety of investigators as to the potential of these organisms needs to be widely disseminated. Over the last few years, it has become obvious from analyses of the published (and, to some extent, unpublished) genomic sequences of a variety of microbes that there are at least a dozen potential biosynthetic clusters in each organism surveyed and, in certain well-publicized cases, over 30 such groupings.[84−92] In the marine environment the interplay of these two sources, as exemplified by the recent review by Newman and Hill,[93] leaves no doubt that a host of novel, bioactive chemotypes await discovery from both terrestrial and marine sources.

In this respect it should be noted that in the last year or so there has been a very significant series of findings where the well-known antitumor agents camptothecin[94] and podophyllotoxin[95] and vincristine[96] have now been produced by fermentation of endophytic fungi, isolated from the producing plants. The usual argument that these are artifacts because of the inability to produce large quantities by regular fermentation processes has been shown to be specious by the work by Bok et al.[84] with *Aspergillus nidulans*. This work demonstrated that one has to be able to find the "genetic on switch" to be able to obtain expression of such clusters outside of the host. In addition to these papers the reader's attention is also drawn to the recent excellent review article by Gunatilaka[97] on this subject, which gives an excellent overview of the numbers of materials so far discovered from these sources. As a result, investigators need to consider all possible routes to novel agents.

To us, a multidisciplinary approach to drug discovery, involving the generation of truly novel molecular diversity from natural product sources, combined with total and combinatorial synthetic methodologies, and including the manipulation of biosynthetic pathways (so-called combinatorial biosynthesis), provides the best solution to the current productivity crisis facing the scientific community engaged in drug discovery and development.

Once more, as we stated in our 2003 review,[2] we strongly advocate *expanding*, not decreasing, the exploration of Nature as a source of novel active agents that may serve as the leads and scaffolds for elaboration into desperately needed efficacious drugs for a multitude of disease indications.

Supporting Information Available: An Excel XP spreadsheet is available free of charge via the Internet at http://pubs.acs.org.

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