Reviews

Natural Products as Sources of New Drugs over the Period 1981−2002

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Received March 7, 2003

This review is an updated and expanded version of a paper that was published in this journal in 1997. The time frame has been extended in both directions to include the 22 years from 1981 to 2002, and a new secondary subdivision related to the natural product source but applied to formally synthetic compounds has been introduced, using the concept 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, the percentage of small molecule, new chemical entities that are nonsynthetic has remained at 62% averaged over the whole time frame. In other areas, the influence of natural product structures is quite marked, particularly in the antihypertensive area, where of the 74 formally synthetic drugs, 48 can be traced to natural product structures/mimics. Similarly, with the 10 antimigraine drugs, seven are based on the serotonin molecule or derivatives thereof. Finally, although combinatorial techniques have succeeded as methods of optimizing structures and have, in fact, been used in the optimization of a number of recently approved agents, we have not been able to identify a *de novo* combinatorial compound approved as a drug in this time frame.

It is over six years since the publication of our first analysis of the sources of new and approved drugs for the treatment of human diseases, which indicated that natural products play a highly significant role in the drug discovery and development process.[1] This was particularly evident in the areas of cancer and infectious diseases, where over 60% and 75% of these drugs, respectively, were shown to be of natural origin. The analysis was based on the numbers of new drugs approved by regulatory agencies [e.g., the United States Food and Drug Administration (FDA)] as reported in *Annual Reports of Medicinal Chemistry* from 1983 to 1994.

Over the past six years since our previous review[1] there has been a rapid escalation in the discovery of molecular targets that may be applied to the discovery of novel tools for the diagnosis, prevention, and treatment of human diseases (http://www.experts.co.uk/molecular_targets.htm). With the sequencing of the human genome, there has been an explosion in the knowledge of the protein products associated with the constituent genes[2] and the discovery of molecular targets associated with various disease types, as, for example, in diabetes and obesity[3] and cancer.[4,5] In addition, the sequencing of the genomes of pathogens and parasites will permit the identification of genes essential for the survival of the pathogens, and their encoded proteins may serve as molecular targets for new drug discovery. Excellent examples are the sequencing of the genomes of the malaria parasite, *Plasmodium falciparum*,[6] and one of the major mosquito vectors, *Anopheles gambiae*,[7] which will provide new tools for the control of this dreaded disease.[8]

The development of high-throughput screens based on molecular targets has led to a demand for the generation of large libraries of compounds to satisfy the enormous capacities of these screens. Combinatorial chemistry, a technology conceived about 20 years ago, was envisaged as the answer to this demand, initially focusing on the synthesis of peptide and oligonucleotide libraries, but now reported to be shifting its focus to the synthesis of small, drug-like molecules.[9] Consequently, many pharmaceutical companies have deemphasized natural products research in favor of high-throughput screening of mass-produced combinatorial libraries, no doubt with the expectation of reaping rich rewards in terms of a multiplicity of novel drugs and the resultant revenue windfalls. The expected surge in productivity, however, has not materialized, and the number of new active substances (NASs), also known as New Chemical Entities (NCEs), has hit a 20-year low of 37 in 2001, and is still declining.[10] As reported by Class, the FDA "had received 16 New Drug Applications in 2001, down from 24 the previous year". As a counterpoint, one should, however, read the two recent reviews from Waldmann's group for further discussions on the intrinsic value of natural products as "leads to new structures with different activities" by using combinatorial synthetic techniques on an already proven biologically active structure.[11,12]

Against this backdrop, we now present an updated analysis of the role of natural products in the drug discovery and development process, dating from 1981 to 2002. As in our earlier analysis, we have consulted *Annual Reports of Medicinal Chemistry*.[13−31] To extend the time frame and to cover other agents not captured in the *Annual Reports of Medicinal Chemistry* from 1983 to 2002, we have also added data from the publication *Drug News and Perspective*[32−44] and extended the search by using the Prous *Ensemble* database, thus permitting us to produce a more comprehensive coverage from 1981 to 2002.

We have also included the relevant references in a condensed form in Tables 3−9; otherwise the numbers of references cited in the review would become overwhelming. In these cases, "ARMC ##" refers to the volume of *Annual*

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10.1021/np030096l
Published on Web 06/12/2003

Table 1. New Chemical Entities and Medical Indications by Source of Compound[a,b]

indication	total	origin of drug						indication	total	origin of drug					
		B	N	ND	S	S*	V			B	N	ND	S	S*	V
analgesic	15				13	2		antiviral	35	2		1	8	24	
anesthetic	5				5			anxiolytic	10				10		
anti-Alzheimer's	4		1		3			benign prostatic hypertrophy	4		1	2	1		
anti-Parkinsonism	10			2	4	4		bronchodilator	8			2		6	
antiallergic	15		1	3	11			calcium metabolism	17			8	9		
antianginal	4				4			cardiotonic	13			3	5	5	
antiarrhythmic	15		1		12	2		chelator & antidote	5				5		
antiarthritic	12	2		1	9			contraception	6			6			
antiasthmatic	12			2	8	2		diuretic	4				4		
antibacterial	90		9	61	19	1		gastroprokinetic	4				3	1	
anticancer	79	12	9	21	25	10	2	hematopoiesis	5	5					
anticoagulant	16	3		12		1		hemophilia	9	9					
antidepressant	21				19	2		hepatitis	17	7				1	9
antidiabetic	23	12	1	2	7	1		hormone	20	10		10			
antiemetic	7				1	6		hormone replacement therapy	4			4			
antiepileptic	10			1	6	3		hypnotic	11				11		
antifungal	24	1		2	21			hypocholesterolemic	9		3	1	2	3	
antiglaucoma	13			4	5	4		hypolipidemic	8		1		7		
antihistamine	12				12			immunostimulant	10	4	3	2	1		
antihyperprolactinemia	4			4				immunosuppressant	10	4	5	1			
antihypertensive	75			1	40	34		muscle relaxant	10			4	3	3	
antiinflammatory	50	1		13	36			neuroleptic	10				8	2	
antimigraine	10				3	7		nootropic	8			3	5		
antiparasitic	13		2	5	4	2		platelet aggregation inhibitor	4			3	1		
antipsoriatic	4			3		1		respiratory distress syndrome	6	3	1		2		
antipsychotic	7				5	2		vasodilator	6			3	3		
antithrombotic	28	13	1	5	7	2		vulnerary	5	2		2	1		
antiulcer	32	1	1	12	18			grand total	868	91	40	209	386	131	11

[a] Where there were ≤3 NCEs per indication in the time frame 1981−2002, the number of NCEs totaled 163. These were assignable as B, 34; N, 10; ND, 31; S, 57; S*, 13; V, 18. [b] The indications for these 163 drugs are as follows: ADHD, β-lactamase inhibitor, CNS stimulant, chronic obstructive pulmonary disease; cystic fibrosis, Crohn's Disease, Gaucher's disease, Lyme disease, PCP/toxoplasmosis, abortifacient, actinic keratoses, adjuvant/colorectal cancer, alcohol deterrent, anabolic metabolism, analeptic, anemia, antismoking, antiacne, antiathersclerotic, anticholelithogenic, anticonvulsant, antidiarrheal, antiemphysemic, antiestrogen, antihyperuricemia, antihypotensive, antinarcolepsy, antinarcotic, antinauseant, antiobesity, antiperistaltic, antiprogestogen, antiprotozoal, antirheumatic, antisecretory, antisepsis, antiseptic, antispasmodic, antispastic, antitussive, antixerostomia, blepharospasm, bone morphogenesis, bowel evacuant, cardioprotective, cardiovascular disease, cervical dystonia, chicken pox, cholera, choleretic, cognition enhancer, congestive heart failure, cystic fibrosis, cytoprotective, diabetic foot ulcers, digoxin toxicity, diphtheria-pertussis-tetanus vaccine, dysuria, enzymic action, erythropoiesis, expectorant, Fabry's disease, female infertility, gastroprotectant, genital warts, *Haemophilus influenzae* infection, hematological, hepatoprotectant, homocystinuria, hyperphenylalaninemia, hypoammonuric, hypocalciuric, hypogonadism, immunomodulator, invasive pneumococci, irritable bowel syndrome, joint lubricant, lipoprotein disorders, male sexual dysfunction, meningococcal C disease, mucolytic, multiple sclerosis, nasal decongestant, neuroprotective, opiate detoxification, pancreatic disorders, pancreatitis, pertussis, photosensitizer, porphyria, premature birth, progestogen, *purpura fulminans*, rattlesnake antivenom, respiratory syncytial virus, rotavirus infection, rubella, sclerosant, secondary hyperthyroidism, sedative, skin photodamage, strabismus, subarachnoid hemorrhage, thrombocytopenia, typhoid prophylaxis, ulcerative colitis, unstable bladder, urea cycle disorders, urolithiasis, urologic, vasoprotective.

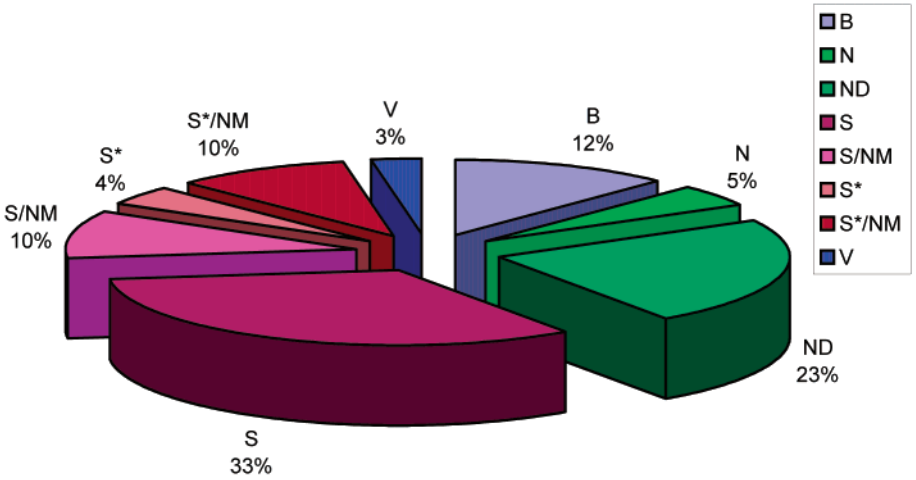


Figure 1. All new chemical entities, 1981−2002, by source (N = 1031).

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 a "P######" is the accession number in the Prous *Ensemble* database. Finally, we have used "Boyd" to refer to a review article[45] on clinical antitumor agents and "M'dale" to refer to *Martindale*[46] 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

Table 2. New Chemical Entities and Medical Indications by Source of Compound with "NM" Subdivisions

		origin of drug							
indication	total	B	N	ND	S	S/NM	S*	S*/NM	V
analgesic	15				11	2	2		
anesthetic	5				5				
anti-Alzheimer's	4		1			3			
anti-Parkinsonism	10			2		4		4	
antiallergic	15		1	3	11				
antianginal	4				4				
antiarrhythmic	15		1		12			2	
antiarthritic	12	2		1	3	6			
antiasthmatic	12			2	2	6		2	
antibacterial	90		9	61	19			1	
anticancer	79	12	9	21	17	8	7	3	2
anticoagulant	16	3		12			1		
antidepressant	21				7	12		2	
antidiabetic	23	12	1	2	3	4	1		
antiemetic	7				1			6	
antiepileptic	10			1	6		2	1	
antifungal	24	1		2	18	3			
antiglaucoma	13			4		5	1	3	
antihistamine	12				12				
antihyper-prolactinemia	4			4					
antihypertensive	75			1	26	14	2	32	
antiinflammatory	50	1		13	36				
antimigraine	10				2	1		7	
antiparasitic	13		2	5	4		2		
antipsoriatic	4			3				1	
antipsychotic	7				3	2		2	
antithrombotic	28	13	1	5	2	5		2	
antiulcer	32	1	1	12	18				
antiviral	35	2		1	7	1	17	7	
anxiolytic	10				8	2			
benign prostatic hypertrophy	4		1	2		1			
bronchodilator	8			2				6	
calcium metabolism	17			8	8	1			
cardiotonic	13			3	2	3		5	
chelator & antidote	5				3	2			
contraception	6			6					
diuretic	4				4				
gastroprokinetic	4				1	2		1	
hematopoiesis	5	5							
hemophilia	9	9							
hepatitis	17	7					1		9
hormone	20	10		10					
hormone replacement therapy	4			4					
hypnotic	11				11				
hypocholesterolemic	9		3	1	2			3	
hypolipidemic	8		1		7				
immunostimulant	10	4	3	2	1				
immunosuppressant	10	4	5	1					
muscle relaxant	10			4	2	1	3		
neuroleptic	10				2	6		2	
nootropic	8			3	5				
platelet aggregation inhibitor	4			3		1			
respiratory distress syndrome	6	3	1		1	1			
vasodilator	6			3	2	1			
vulnerary	5	2		2	1				
grand total	868	91	40	209	289	97	39	92	11

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 only covered 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 past 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 low tens per year for the last five or so years (see Figures 2 and 5).

As in our original analysis[1] the data have been analyzed in terms of numbers and classified according to their origin using the previous major categories with the addition of a separate listing for vaccines. We have, however, felt the need to add an extra subcategory, "NM" (Natural Product Mimic), to indicate those drugs, under both the "S*" and "S" major subdivisions that, though totally synthetic, either are modeled on a natural product inhibitor of the molecular target of interest or mimic (i.e., competitively inhibit) the endogenous substrate of an active site, such as ATP, adrenergic amines, and endothelins. The rationale for such a subdivision is elaborated in a later section.

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.

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

One subcategory is used.

"NM": Natural Product Mimic (see rationale and examples below).

Rationale for the Use of the Subclassification of "NM" or "Natural Product Mimic". One of the more interesting meta-analyses that can be performed on the structural data that we have assembled is to attempt to decide whether a given compound or series of similar compounds is derived from knowledge gained from a study of the original natural product-derived drug or, more usually, lead or initial hit, even though the final product of such a synthetic campaign may not bear much, if any, resemblance to the original natural product. As a result of such an analysis, we have given the subdesignation "NM" to a fairly substantial number of compounds that apparently fall into the category of "designed from knowledge gained from a natural product" or, in some cases, "discovered by using an assay whereby the compound is designed to displace the natural substrate in a competitive fashion", and are thus "Natural Product Mimics" or "NM". In practice, both methods and other information such as X-ray binding studies (*ab initio* or *in silico*), may well be involved in the derivation of the final drug.

There are two limit cases, representing an obvious natural product relationship at one extreme, to the nonobvious cases at the opposite extreme, that can be considered in such analyses. In the first, where the drug entity is considered to be an "S*" (totally synthetic but based on a natural product pharmacophore), the relationship may be relatively obvious. Examples would be the ACE inhibitors that were designed to mimic the C-terminal sequence of angiotensin I (AT I) and thus prevent the production of

Table 3. Antibacterial Drugs from 1981 to 2002 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	reference	page	source
carumonam	Amasulin	1988	ARMC 24	298	N
fosfomycin trometamol	Monuril	1988	P112334		N
isepamicin	Isepacin	1988	ARMC 24	305	N
micronomicin sulfate	Sagamicin	1982	P091082		N
miokamycin	Miocamycin	1985	ARMC 21	329	N
mupirocin	Bactroban	1985	ARMC 21	330	N
netilimicin sulfate	Netromicine	1981	P070366		N
RV-11	Zalig	1989	ARMC 25	318	N
teicoplanin	Targocid	1988	ARMC 24	311	N
apalcillin sodium	Lumota	1982	P091130		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
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 hydrochloride	Globocef	1992	ARMC 28	327	ND
cefixime	Cefspan	1987	ARMC 23	329	ND
cefmenoxime hydrochloride	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	P127130		ND
ceforanide	Precef	1984	ARMC 20	317	ND
cefoselis	Wincef	1998	ARMC 34	319	ND
cefotetan disodium	Yamatetan	1984	ARMC 20	317	ND
cefotiam hydrochloride	Pansporin	1981	P091106		ND
cefozopran hydrochloride	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	P091108		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	P070260		ND
ceftriaxone sodium	Rocephin	1982	P091136		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
ertapenem sodium	Invanz	2002	*P*236885		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 hydrochloride	Varacillin	1987	ARMC 23	336	ND
loracarbef	Lorabid	1992	ARMC 28	333	ND
meropenem	Merrem	1994	ARMC 30	303	ND
moxalactam disodium	Shiomarin	1982	P070301		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
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
grepafloxacin	Vaxor	1997	DNP 11	23	S
levofloxacin	Floxacin	1993	ARMC 29	340	S

Table 3 (Continued)

generic name	trade name	year introduced	reference	page	source
linezolid	Zyvox	2000	DNP 14	21	S
lomefloxacin	Uniquin	1989	ARMC 25	315	S
moxifloxacin hydrochloride	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
pefloxacin mesylate	Perflacine	1985	ARMC 21	331	S
rufloxacin hydrochloride	Qari	1992	ARMC 28	335	S
sparfloxacin	Spara	1993	ARMC 29	345	S
taurolidine	Taurolin	1988	P107771		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

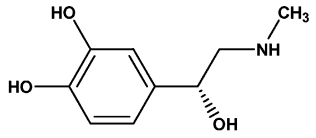
angiotensin II (AT II) by removal of the C-terminal dipeptide following the work originally started from studies on teprotide.[47] Another obvious example would be the β-blockers or β-agonists (selective or general) that are modeled upon the biogenic amines, and the subsets of dopamine receptor antagonists and serotonin receptor blockers derived from the base dopamine or serotonin structures (with modifications to aid in binding). In these cases (structures **1**−**6**), the structural relationships are relatively obvious. We have identified the mechanism of action of all compounds that fall into the "S*/NM" subcategory, and these are available in database format from the authors.

In the second limit case, those compounds classified as "S" for totally synthetic, the relationships are frequently nonobvious and require some "*structural forensics*" to determine any relationship to a natural product. Where they have been identified by direct competitive assays against the natural product substrate, the relationship will be similar to the second "S*/NM" case discussed above, i.e., where there is a direct displacement of the natural substrate. However, in a number of cases the genesis of the synthetic drug can be derived directly from publications, and one can show how the compound(s) evolved from the natural product(s) structural information.

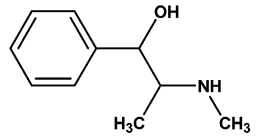
Perhaps the best examples to consider initially are those derived from the use of peptide isosteres and pseudopeptides (peptidomimetics), as the final product(s) in these cases bear little formal structural relationship to the original peptide(s). There are a series of excellent reviews, one published in 1993[48] and the others in 2002,[49−51] that can aid materially in this type of study, and we recommend that readers who are interested in this aspect of the analyses consult them in detail.

One example that demonstrates the point is the history of the angiotensin II receptor (AT1R) blocker, losartan, which we define as an "S/NM", both on the basis of its mechanism/assay and, in particular, from the following discussion. In this discussion there is a potential for confusion. The conventional shorthand biochemical designation for the pharmacologically active octapeptide that results from the action of angiotensin-converting enzyme (ACE) upon the decapeptide angiotensin I (or AT I) is AT II. However, from biochemical pharmacology nomenclature, the receptor for this octapeptide ligand is designated as the angiotensin 1 receptor (AT1R). Thus, AT1R is the receptor for the octapeptide AT II, the active ligand produced by ACE action upon angiotensin I (AT I), not, as some may expect, the receptor for the ACE substrate, AT I.

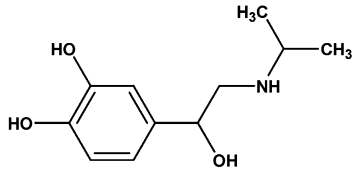
From structure activity (SAR) studies on multiple peptide analogues of the octapeptide AT II, whose formal sequence is H_2N-Asp^1-Arg^2-Val^3-Tyr^4-Ile^5-His^6-Pro^7-Phe^8-CO_2H, there were suggestions that the His^6 residue was required for receptor recognition and that the agonist activity required the phenyl ring of the Phe^8, the hydroxyl group of the Tyr^4, and the C-terminal carboxylate. Thus, a working hypothesis for the binding pocket in AT1R for the ligand, AT II, would be a positively charged site, a lipophilic pocket or pockets, and a hydrogen bond acceptor.[52]



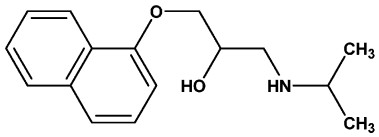
1 Epinephrine



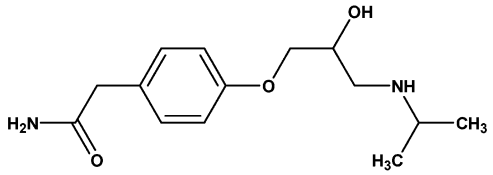
2 Ephedrine



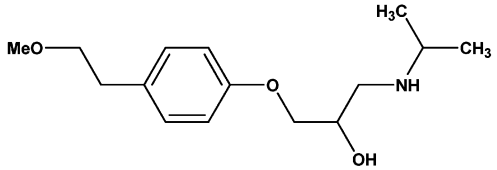
3 Isoprenaline



4 Propranolol



5 Atenolol

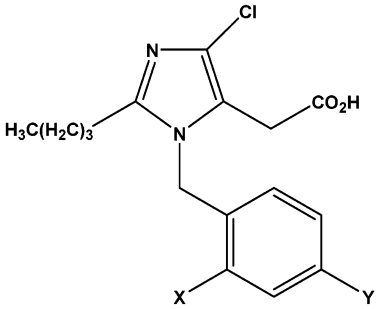


6 Metaprolol

Table 4. Antifungal Drugs from 1981 to 2002 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
caspofungin acetate	Cancidas	2001	DNP 15	36	ND
micafungin sodium	Fungard	2002	P263634		ND
amorolfine hydrochloride	Loceryl	1991	ARMC 27	322	S
butoconazole	Femstat	1986	ARMC 22	318	S
ciclopirox olamine	Loprox	1982	P070449		S
cloconazole hydrochloride	Pilzcin	1986	ARMC 22	318	S
fenticonazole nitrate	Lomexin	1987	ARMC 23	334	S
fluconazole	Diflucan	1988	ARMC 24	303	S
flutrimazole	Micetal	1995	ARMC 31	343	S
itraconazole	Sporanox	1988	ARMC 24	305	S
ketoconazole	Nizoral	1981	P116505		S
lanoconazole	Astat	1994	ARMC 30	302	S
naftifine hydrochloride	Exoderil	1984	ARMC 20	321	S
neticonazole hydrochloride	Atolant	1993	ARMC 29	341	S
oxiconazole nitrate	Oceral	1983	ARMC 19	322	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	P179738		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

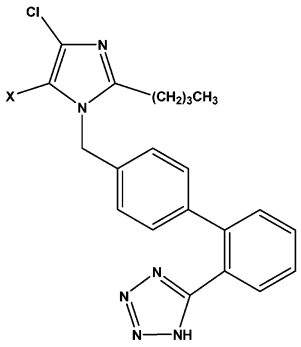
The first lead to a nonpeptidic structure that demonstrated AT1R inhibition was actually from nature. In 1982, workers at Takeda reported in a U.S. patent[53] the structures of three microbial metabolites (structures **7**−**9**) that



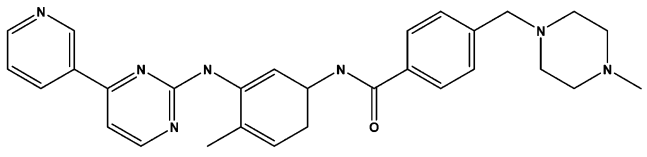
7 X = NO_2 Y = H
8 X= Cl; Y = H
9 X= H; Y = H
10 X = H; Y= CO_2H

had low potency as antihypertensive agents. Using simple modeling methods, both Dreiding models and simple computerized techniques, workers at DuPont postulated that these compounds, which at high concentrations demonstrated a small reduction in blood pressure via blockade of AT1R, bound to the receptor in a manner such that the carboxylic acid was equivalent to the C-terminal carboxylate of AT II; the imidazole nitrogens were comparable with the histidine residue; and the benzyl group pointed toward the N-terminus of AT II, with the *para* position of that residue holding the most promise for a systematic extension toward the amino-terminus of AT II. By making the (correct) assumption that a second carboxylate in the *para* position of the phenyl ring would give a negative charge in the vicinity of the Tyr^4 hydroxyl and the Asp^1 β-carboxylic acid, the compound was prepared (structure **10**) and demonstrated a 10-fold increase in binding affinity. The rest of the story of the derivation of what finally became the first approved AT1R antagonist (losartan) is told in three excellent papers by the DuPont group[52,54,55] with a clinical efficacy review in 1996 in the *New England Journal of Medicine*,[56] and recently an excellent QSAR study of this and later drugs with a similar mechanism of action (MOA) has been published by Hansch and associates.[57]

The structures of losartan (**11**) and its more active metabolite, EXP3174 (**12**), where the hydroxymethylene substituent in losartan is oxidized *in vivo* to give the carboxylate, thereby mimicking the "first" derivative (**10**) of the microbial metabolites referred to earlier, are shown.



11 Losartan; X = CH_2OH
12 EXP3174; X = CO_2H



13 Gleevec

In the field of anticancer therapy, the advent in 2001 of Gleevec (**13**), a protein tyrosine kinase inhibitor, was justly heralded as a breakthrough in the treatment of leukemia. This compound, too, can be classified as an "NM" on the basis of its competitive displacement of the natural substrate, ATP. The fundamental substrate of all protein kinases (PKs) is the ubiquitous biochemical compound ATP, whose intracellular concentrations can approach 5 mM. With over 2000 PKs identified/postulated from biochemical and genetic evidence by 1994, the prevailing

Table 5. Antiviral Drugs from 1981 to 2002 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	reference	page	source
interferon alfa-n3	Alferon N	1990	DNP 04	104	B
interferon alfacon-1	Intergen	1997	ARMC 33	336	B
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 hydrochloride	Roflual	1987	ARMC 23	342	S
abacavir sulfate	Ziagen	1999	ARMC 35	333	S*
acyclovir	Zovirax	1981	P091119		S*
cidofovir	Vistide	1996	ARMC 32	306	S*
didanosine	Videx	1991	ARMC 27	326	S*
epervudine	Hevizos	1988	P157373		S*
famciclovir	Famvir	1994	ARMC 30	300	S*
ganciclovir	Cymevene	1988	ARMC 24	303	S*
inosine pranobex	Imunovir	1981	P277341		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 hydrochloride	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
fomivirsen sodium	Vitravene	1998	ARMC 34	323	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
oseltamivir	Tamiflu	1999	ARMC 35	346	S/NM

dogma for a significant number of years was that one could not obtain selectivity with inhibitors that targeted the ATP binding site because of the ubiquity of the enzymes and substrate. The number of PKs has certainly increased since then,[58] and with the discovery of significant (often relatively selective) inhibition of a variety of protein kinases by many different natural products and derivatives thereof, the dogma has changed.[58]

Novartis (originally at Ciba-Geigy) discovered the phenylaminopyrimidine (PAP) structure in a screen for selective inhibitors of protein kinase C (PKC), but introduction of a methyl group in the phenyl ring *ortho* to the aminopyrimidine substituent switched activity from PKC and Cyclin-dependent Kinase 1 (Cdk1) inhibition toward inhibition of the *abl*, *c-kit*, and PDGF-R kinases.[59] The ultimate pharmacophore development and site of binding of Gleevec (STI571) is elegantly described by the Novartis team in a recent review, which also covers other PTK inhibitors.[4] The essential point from our aspect, however, is that Gleevec is a "competitive inhibitor of ATP with a K_i of 85 nM against *Abl*", thus confirming that it binds directly at the ATP site.[4] There is an excellent schematic of how this compound fits into the kinase domain in the same review, together with the reason that a point mutation in this domain causes resistance to the drug.

There are many other examples in the literature describing how formally nonpeptidic compounds have been synthesized as competitive inhibitors of the naturally occurring peptide substrates, and unless one actually searches for the original lead peptidic structure, these compounds are destined to be classified as synthetics. As mentioned earlier in the section, interested readers should consult the recent reviews on this subject.[49−51]

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, one should consult the recent review by the Pittsburgh group on dual-specificity phosphatases.[60] A further example is the conversion of the natural product galanthamine (which is an approved anti-Alzheimer's drug) into the novel agent secramine, with an entirely different MOA.[61] Other examples demonstrating the power of coupling natural product-based structures with combinatorial methods are given in the recent reviews by Kingston and Newman,[58] and Nielsen.[62]

Overview of Results

The data we have analyzed in a variety of ways are presented in 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 1981−2002:

- New Approved Drugs: With all source categories (Figure 1)
- New Approved Drugs: By source/year (Figure 2)
- Sources of all NCEs: Where four or more drugs were approved per medical indication (Tables 1 and 2)
- Sources of nonbiological NCEs: With "NM" subdivisions (Figure 3) and without (Figure 4)
- Sources of nonbiological NCEs: By source/year (Figure 5)
- Antibacterial Drugs: Generic and trade names, year, reference, and source (Table 3)

Table 6. Anticancer Drugs from 1981 to 2002 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	reference	page	source
alemtuzumab	Campath	2001	DNP 15	38	B
celmoleukin	Celeuk	1992	DNP 06	102	B
denileukin diftitox	Onlak	1999	ARMC 35	338	B
interferon alfa2a	Roferon-A	1986	P204503		B
interferon, gamma-1a	Biogamma	1992	ARMC 28	332	B
interleukin-2	Proleukin	1989	ARMC 25	314	B
pegaspargase	Oncaspar	1994	ARMC 30	306	B
OCT-43	Octin	1999	ARMC 35	345	B
rituximab	Rituxan	1997	DNP 11	25	B
tasonermin	Beromun	1999	ARMC 35	349	B
teceleukin	Imumace	1992	DNP 06	102	B
trastuzumab	Herceptin	1998	DNP 12	35	B
aclarubicin	Aclacin	1981	P090013		N
angiotensin II	Delivert	1994	ARMC 30	296	N
arglabin	none reported[a]	1999	ARMC 35	335	N
BEC	Curaderm	1989	DNP 03	25	N
masoprocol	Actinex	1992	ARMC 28	333	N
paclitaxel	Taxol	1993	ARMC 29	342	N
pentostatin	Nipent	1992	ARMC 28	334	N
peplomycin	Pepleo	1981	P090889		N
solamargine	Curaderm	1987	P142113		N
alitretinoin	Panretin	1999	ARMC 35	333	ND
amrubicin hydrochloride	Calsed	2002	P142668		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	P091123		ND
epirubicin hydrochloride	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	P177872		ND
gemtuzumab ozogamicin	Mylotarg	2000	DNP 14	23	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
topotecan hydrochloride	Hycamptin	1996	ARMC 32	320	ND
triptorelin	Decapeptyl	1986	P090485		ND
valrubicin	Valstar	1999	ARMC 35	350	ND
vinorelbine	Navelbine	1989	ARMC 25	320	ND
zinostatin stimalamer	Smancs	1994	ARMC 30	313	ND
aminoglutethimide	Cytadren	1981	P070408		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
zoledronic acid	Zometa	2000	DNP 14	24	S
capecitabine	Xeloda	1998	ARMC 34	319	S*
carmofur	Mifurol	1981	P091100		S*
doxifluridine	Furtulon	1987	ARMC 23	332	S*
enocitabine	Sunrabin	1983	ARMC 19	318	S*
fludarabine phosphate	Fludara	1991	ARMC 27	327	S*
gemcitabine hydrochloride	Gemzar	1995	ARMC 31	344	S*
mitoxantrone hydrochloride	Novantrone	1984	ARMC 20	321	S*
bexarotene	Targretine	2000	DNP 14	23	S*/NM
raltitrexed	Tomudex	1996	ARMC 32	315	S*/NM
temozolomide	Temodal	1999	ARMC 35	350	S*/NM
anastrozole	Arimidex	1995	ARMC 31	338	S/NM
bicalutamide	Casodex	1995	ARMC 31	338	S/NM
camostat mesylate	Foipan	1985	ARMC 21	325	S/NM
fadrozole hydrochloride	Afema	1995	ARMC 31	342	S/NM
gefitinib	Iressa	2002	*P*233069		S/NM
imatinib mesilate	Gleevec	2001	DNP 15	38	S/NM
letrazole	Femara	1996	ARMC 32	311	S/NM

Table 6 (Continued)

generic name	trade name	year introduced	reference	page	source
toremifene	Fareston	1989	ARMC 25	319	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 Ensemble database. [b] A prodrug of etoposide.

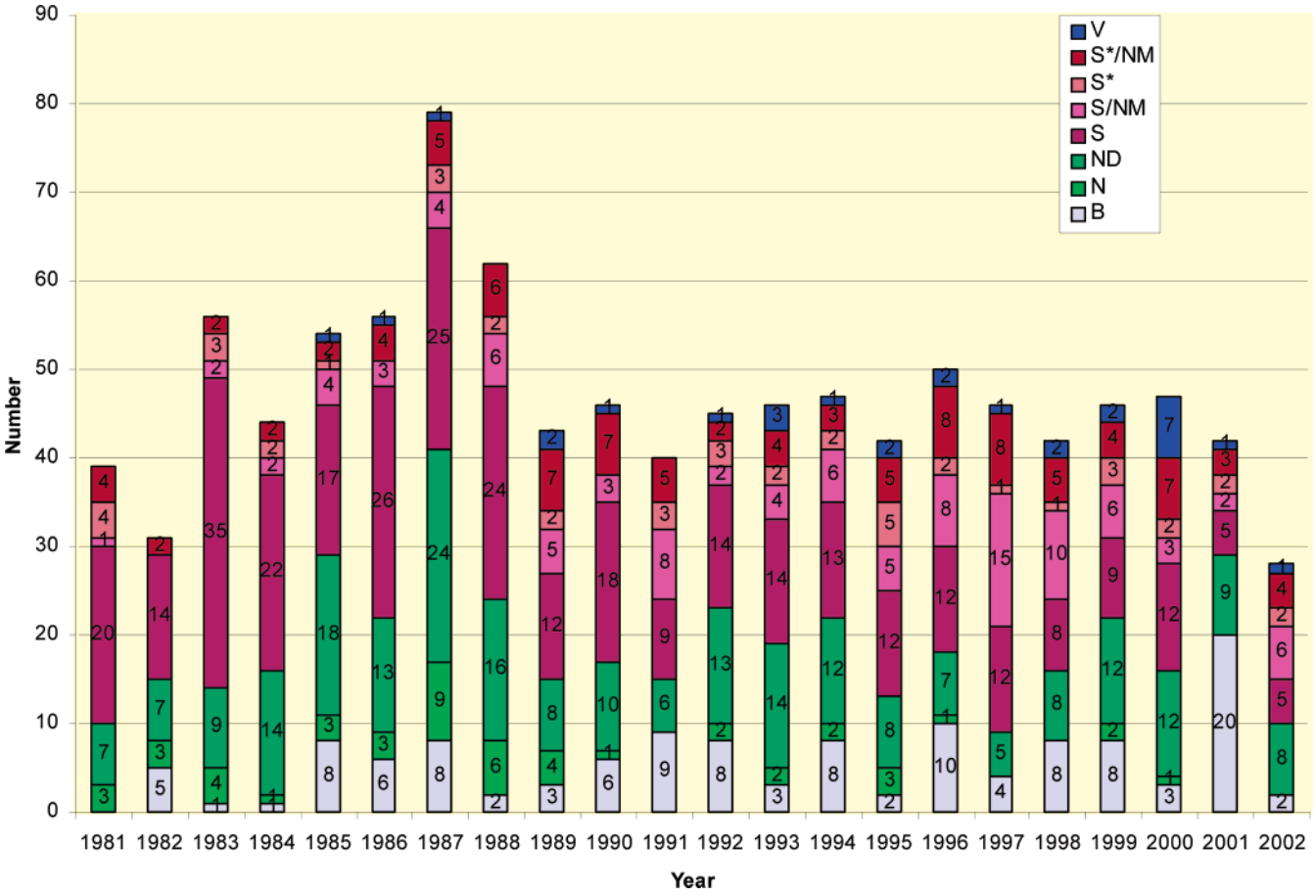


Figure 2. All new chemical entities organized by source/year, with "NM" subdivision ($N = 1031$).

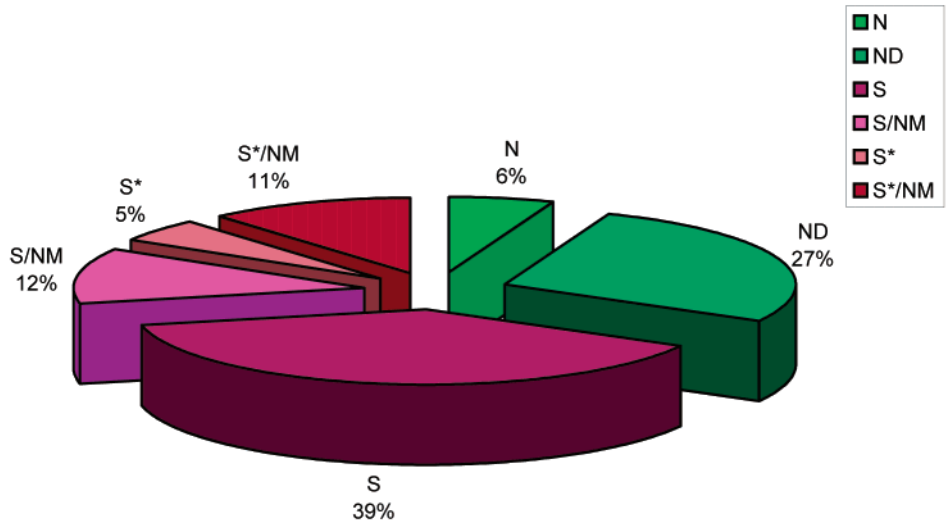


Figure 3. All small molecule new chemical entities, 1981−2002, by source with "NM" subdivision ($N = 877$).

- Antifungal Drugs: Generic and trade names, year, reference, and source (Table 4)
- Antiviral Drugs: Generic and trade names, year, reference, and source (Table 5)
- Anticancer Drugs: Generic and trade names, year, reference, and source (Table 6)
- All Anticancer Drugs (1940s−2002): Generic names, reference, and source (Figures 6 and 7; Table 7)

Table 7. All Anticancer Drugs (1940s−2002) Organized Alphabetically by Generic Name within Source

generic name	year introduced	reference	page	source	generic name	year introduced	reference	page	source
alemtuzumab	2001	DNP 15	38	B	aminoglutethimide	1981	P070408		S
celmoleukin	1992	DNP 06	102	B	amsacrine	1987	ARMC 23	327	S
denileukin diftitox	1999	ARMC 35	338	B	arsenic trioxide	2000	DNP 14	23	S
interferon alfa2a	1986	P204503		B	bisantrene hydrochloride	1990	ARMC 26	300	S
interferon, gamma-1a	1992	ARMC 28	332	B	busulfan	Pre-1981	Boyd		S
interleukin-2	1989	ARMC 25	314	B	camostat mesylate	1985	ARMC 21	325	S
OCT-43	1999	ARMC 35	345	B	carboplatin	1986	ARMC 22	318	S
pegaspargase	1994	ARMC 30	306	B	carmustine	Pre-1981	Boyd		S
rituximab	1997	DNP 11	25	B	chlorambucil	Pre-1981	Boyd		S
tasonermin	1999	ARMC 35	349	B	chlortrianisene	Pre-1981	Boyd		S
teceleukin	1992	DNP 06	102	B	cis-diamminedichloro-platinum	Pre-1981	Boyd		S
trastuzumab	1998	DNP 12	12	B	cyclophosphamide	Pre-1981	Boyd		S
aclarubicin	1981	P090013		N	dacarbazine	Pre-1981	Boyd		S
actinomycin D	Pre-1981	Boyd		N	diethylstilbestrol	Pre-1981	Boyd		S
angiotensin II	1994	ARMC 30	296	N	flutamide	1983	ARMC 19	318	S
arglabin	1999	ARMC 35	335	N	fotemustine	1989	ARMC 25	313	S
asparaginase	Pre-1981	Boyd		N	heptaplatin/SK-2053R	1999	ARMC 35	348	S
BEC	1989	DNP 03	25	N	hexamethylmelamine	Pre-1981	Boyd		S
bleomycin	Pre-1981	Boyd		N	hydroxyurea	Pre-1981	Boyd		S
daunomycin	Pre-1981	Boyd		N	ifosfamide	Pre-1981	Boyd		S
doxorubicin	Pre-1981	Boyd		N	levamisole	Pre-1981	Boyd		S
masoprocol	1992	ARMC 28	333	N	lobaplatin	1998	DNP 12	35	S
mithramycin	Pre-1981	Boyd		N	lomustine	Pre-1981	Boyd		S
mitomycin C	Pre-1981	Boyd		N	lonidamine	1987	ARMC 23	337	S
paclitaxel	1993	ARMC 29	342	N	mechlorethanamine	Pre-1981	Boyd		S
pentostatin	1992	ARMC 28	334	N	melphalan	Pre-1981	Boyd		S
peplomycin	1981	P090889		N	mitotane	Pre-1981	Boyd		S
solamargine	1987	P142113		N	mustine hydrochloride		M'dale 33	561	S
streptozocin	Pre-1981	Boyd		N	nedaplatin	1995	ARMC 31	347	S
testosterone	Pre-1981	Boyd		N	nilutamide	1987	ARMC 23	338	S
vinblastine	Pre-1981	Boyd		N	nimustine hydrochloride	Pre-1981	M'dale 33	562	S
vincristine	Pre-1981	Boyd		N	oxaliplatin	1996	ARMC 32	313	S
alitretinoin	1999	ARMC 35	333	ND	pipobroman	Pre-1981	Boyd		S
amrubicin hydrochloride	2002	P142668		ND	porfimer sodium	1993	ARMC 29	343	S
cladribine	1993	ARMC 29	335	ND	procarbazine	Pre-1981	Boyd		S
cytarabine ocfosfate	1993	ARMC 29	335	ND	ranimustine	1987	ARMC 23	341	S
docetaxel	1995	ARMC 31	341	ND	sobuzoxane	1994	ARMC 30	310	S
dromostanolone	Pre-1981	Boyd		ND	thiotepa	Pre-1981	Boyd		S
elliptinium acetate	1983	P091123		ND	triethylenemelamine	Pre-1981	Boyd		S
epirubicin hydrochloride	1984	ARMC 20	318	ND	uracil mustard	Pre-1981	Boyd		S
estramustine	Pre-1981	Boyd		ND	zoledronic acid	2000	DNP 14	24	S
ethinyl estradiol	Pre-1981	Boyd		ND	aminogluethimide	Pre-1981	Boyd		S*
etoposide	Pre-1981	Boyd		ND	capecitabine	1998	ARMC 34	319	S*
etoposide phosphate[a]	1996	DNP 10	13	ND	carmofur	1981	P091100		S*
exemestane	1999	DNP 13	46	ND	cytosine arabinoside	Pre-1981	Boyd		S*
fluoxymesterone	Pre-1981	Boyd		ND	doxifluridine	1987	ARMC 23	332	S*
formestane	1993	ARMC 29	29	ND	enocitabine	1983	ARMC 19	318	S*
fulvestrant	2002	P177872		ND	floxuridine	Pre-1981	Boyd		S*
gemtuzumab ozogamicin	2000	DNP 14	23	ND	fludarabine phosphate	1991	ARMC 27	327	S*
hydroxyprogesterone	Pre-1981	Boyd		ND	fluorouracil	Pre-1981	Boyd		S*
idarubicin hydrochloride	1990	ARMC 26	303	ND	gemcitabine hydrochloride	1995	ARMC 31	344	S*
irinotecan hydrochloride	1994	ARMC 30	301	ND	goserelin acetate	Pre-1981	Boyd		S*
medroxyprogesterone acetate	Pre-1981	Boyd		ND	leuprolide	Pre-1981	Boyd		S*
megesterol acetate	Pre-1981	Boyd		ND	mercaptopurine	Pre-1981	Boyd		S*
methylprednisolone	Pre-1981	Boyd		ND	methotrexate	Pre-1981	Boyd		S*
methyltestosterone	Pre-1981	Boyd		ND	mitoxantrone hydrochloride	1984	ARMC 20	321	S*
miltefosine	1993	ARMC 29	340	ND	tamoxifen	Pre-1981	Boyd		S*
mitobronitol		M'dale 33	557	ND	thioguanine	Pre-1981	Boyd		S*
pirarubicin	1988	ARMC 24	309	ND	bexarotene	2000	DNP 14	23	S*/NM
prednisolone	Pre-1981	Boyd		ND	raltitrexed	1996	ARMC 32	315	S*/NM
prednisone	Pre-1981	Boyd		ND	temozolomide	1999	ARMC 35	350	S*/NM
teniposide		M'dale 33	574	ND	anastrozole	1995	ARMC 31	338	S/NM
testolactone	Pre-1981	Boyd		ND	bicalutamide	1995	ARMC 31	338	S/NM
topotecan hydrochloride	1996	ARMC 32	320	ND	camostat mesylate	1985	ARMC 21	325	S/NM
triamcinolone	Pre-1981	Boyd		ND	fadrozole hydrochloride	1995	ARMC 31	342	S/NM
triptorelin	1986	P090485		ND	gefitinib	2002	P233069		S/NM
valrubicin	1999	ARMC 35	350	ND	imatinib mesilate	2001	DNP 15	38	S/NM
vindesine		M'dale 33	580	ND	letrazole	1996	ARMC 32	311	S/NM
vinorelbine	1989	ARMC 25	320	ND	toremifene	1989	ARMC 25	319	S/NM
zinostatin stimalamer	1994	ARMC 30	313	ND	bcg live	1990	DNP 04	104	V
					melanoma theraccine	2001	DNP 15	38	V

[a] Prodrug (not counted).

Table 8. Antihypertensive Drugs from 1981 to 2002 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	reference	page	source
treprostinil sodium	Remodulin	2002	P157437		ND
alfuzosin hydrochloride	Xatral	1988	ARMC 24	296	S
amlodipine besylate	Istin	1990	ARMC 26	298	S
arandipine	Bec/Sapresta	1996	ARMC 32	306	S
barnidipine hydrochloride	Hypoca	1992	ARMC 28	326	S
benidipine hydrochloride	Coniel	1991	ARMC 27	322	S
budralazine	Buteraxine	1983	ARMC 19	315	S
cadralazine	Cadraten	1988	ARMC 24	298	S
cicletanine	Tenstaten	1988	ARMC 24	299	S
cinildipine	Cinalong	1995	ARMC 31	339	S
efonidipine hydrochloride	Landel	1994	ARMC 30	299	S
felodipine	Plendil	1988	ARMC 24	302	S
guanadrel sulfate	Hylorel	1983	ARMC 19	319	S
isradipine	Prescal	1989	ARMC 25	315	S
lacidipine	Lacipil	1991	ARMC 27	330	S
lercanidipine	Lerdip	1997	ARMC 33	337	S
manidipine hydrochloride	Calslot	1990	ARMC 26	304	S
mibefradil hydrochloride	Posicor	1997	ARMC 33	338	S
nicardipine hydrochloride	Perpidine	1981	P091152		S
nilvadipine	Nivadil	1989	ARMC 25	316	S
nisoldipine	Baymycard	1990	ARMC 26	306	S
nitrendipine	Bayotensin	1985	ARMC 21	331	S
pinacidil	Pindac	1987	ARMC 23	340	S
rilmenidine	Hyperium	1988	ARMC 24	310	S
terazocin hydrochloride	Hytrin	1984	ARMC 20	323	S
tiamenidine hydrochloride	Sundralen	1988	ARMC 24	311	S
urapidil	Ebrantil	1981	P172318		S
celiprolol hydrochloride	Selectol	1983	ARMC 19	317	S*
indoramin hydrochloride	Wydora	1981	P091274		S*
alacepril	Cetapril	1988	ARMC 24	296	S*/NM
amosulalol	Lowgan	1988	ARMC 24	297	S*/NM
arotinolol hydrochloride	Almarl	1986	ARMC 22	316	S*/NM
benazepril hydrochloride	Cibacen	1990	ARMC 26	299	S*/NM
betaxolol hydrochloride	Kerlone	1983	ARMC 19	315	S*/NM
bevantolol hydrochloride	Ranestol	1987	ARMC 23	328	S*/NM
bisoprolol fumarate	Concor	1986	ARMC 22	317	S*/NM
bopindolol	Sandonorm	1985	ARMC 21	324	S*/NM
carvedilol	Dilatrend	1991	ARMC 27	323	S*/NM
cilazapril	Inhibace	1990	ARMC 26	301	S*/NM
cloranolol hydrochloride	Tobanum	1981	P115093		S*/NM
delapril	Adecut	1989	ARMC 25	311	S*/NM
dilevalol	Levadil	1989	ARMC 25	311	S*/NM
enalapril maleate	Reniten	1984	ARMC 20	317	S*/NM
enalaprilat	Renitec	1987	ARMC 23	332	S*/NM
fosinopril sodium	Staril	1991	ARMC 27	328	S*/NM
imidapril hydrochloride	Tanatril	1993	ARMC 29	339	S*/NM
lisinopril	Prinivil	1987	ARMC 23	337	S*/NM
mepindolol sulfate	Corindolan	1981	P091107		S*/NM
moexipril hydrochloride	Univasc	1995	ARMC 31	346	S*/NM
moxonidine	Cynt	1991	ARMC 27	330	S*/NM
nipradilol	Hypadil	1988	ARMC 24	307	S*/NM
penbutanol sulfate	Betapressin	1981	P091512		S*/NM
perindopril	Coversyl	1988	ARMC 24	309	S*/NM
quinapril	Accupro	1989	ARMC 25	317	S*/NM
ramipril	Triatec	1989	ARMC 25	317	S*/NM
spirapril hydrochloride	Setrilan	1995	ARMC 31	349	S*/NM
temocapril hydrochloride	Acecol	1994	ARMC 30	311	S*/NM
tertatolol hydrochloride	Artex	1987	ARMC 23	344	S*/NM
tilisolol hydrochloride	Daim	1992	ARMC 28	337	S*/NM
trandolapril	Odrik	1993	ARMC 29	348	S*/NM
zofenapril calcium	Zantipres	2000	DNP 14	16	S*/NM
bosentan	Tra-cleer	2001	DNP 15	32	S/NM
bunazosin hydrochloride	Detandol	1985	ARMC 21	324	S/NM
candesartan cilexetil	Atacand	1997	ARMC 33	330	S/NM
doxazosin mesylate	Carduran	1988	ARMC 24	300	S/NM
eprosartan	Teveten	1997	ARMC 33	333	S/NM
fenoldopam mesylate	Corlopam	1998	ARMC 34	322	S/NM
irbesartan	Avapro	1997	ARMC 33	336	S/NM
ketanserin	Serefrex	1985	ARMC 21	328	S/NM
losartan potassium	Cozaar	1994	ARMC 30	302	S/NM
nebivolol	Nebilet	1997	ARMC 33	339	S/NM
olmesartan medoxil	Benicar	2002	P217950		S/NM
telmisartan	Micardis	1999	ARMC 35	349	S/NM
trimazosin hydrochloride	Supres	1985	ARMC 21	333	S/NM
valsartan	Diovan	1996	ARMC 32	320	S/NM

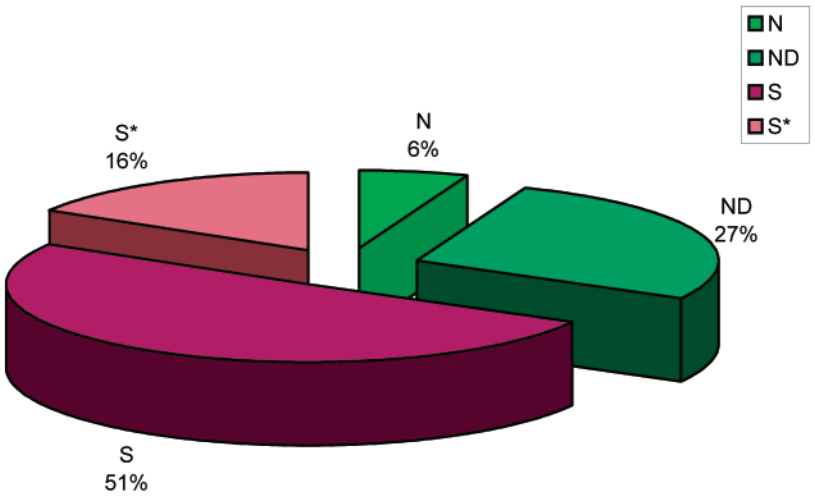


Figure 4. All small molecule new chemical entities, 1981−2002, by source without "NM" subdivision (N = 877).

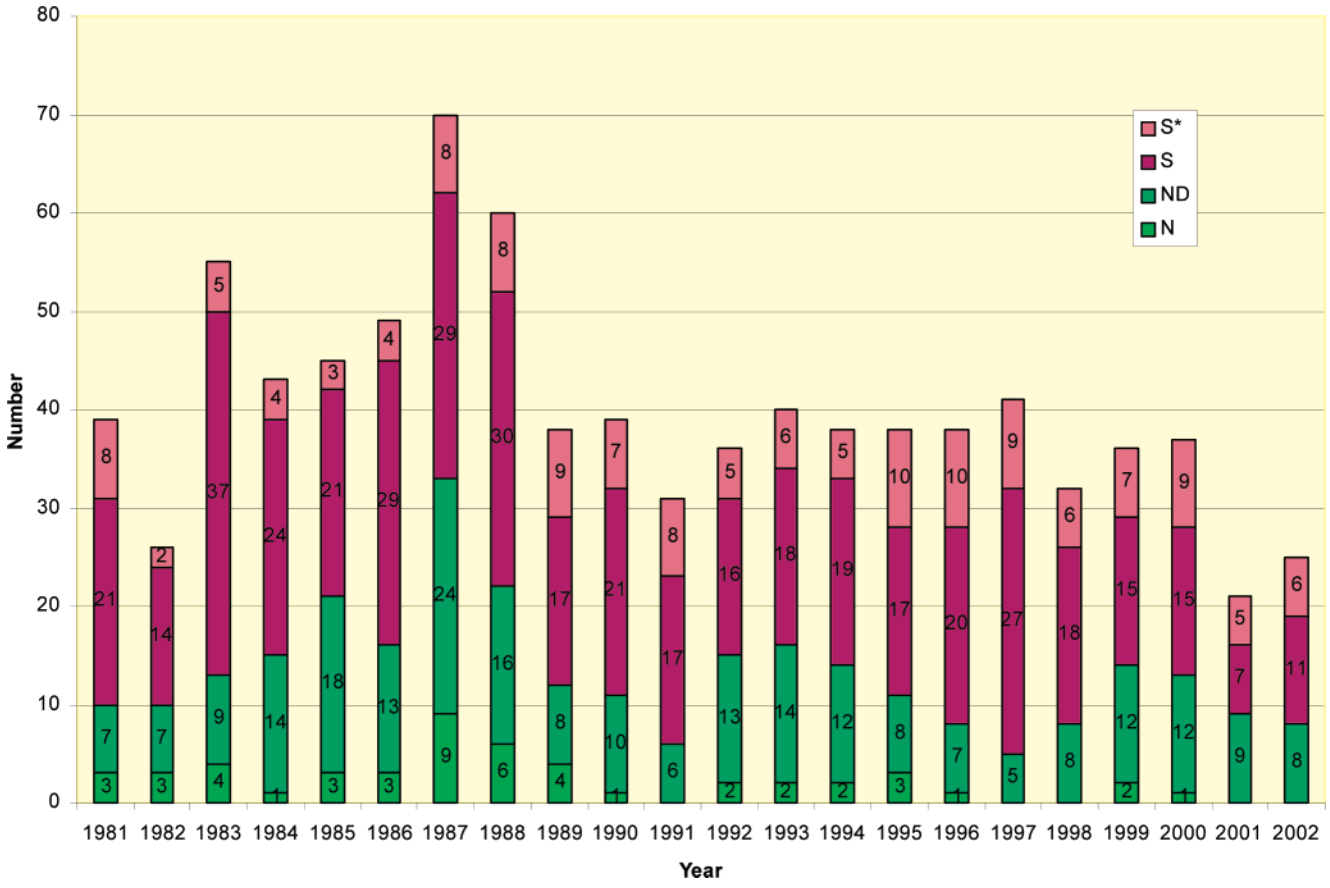


Figure 5. Small molecule new chemical entities organized by source/year, without "NM" subdivision (N = 877).

• Antihypertensive Drugs: Generic and trade names, year, reference, and source (Table 8)

• Antimigraine Drugs: Generic and trade names, year, reference, and source (Table 9)

The extensive data sets shown in the figures and tables referred to above highlight the continuing role that natural products and structures derived from/related to natural products from all sources have played and continue to play in the current therapeutic armamentarium of the physician. Inspection of the data shows this continued important role for natural products despite the current reduction of natural products-based drug discovery programs in pharmaceutical houses with a few notable exceptions.

Inspection of the rate of NCE approvals as shown in Figure 2 demonstrates that, despite many years of efforts on the part of the pharmaceutical industry in high-throughput screening of (predominately) combinatorial chemistry products, in the years 2000, 2001, and 2002 (which should have provided a sufficient timespan for early efforts in the late 1980s and early 1990s to have produced approved NCEs), the natural products field is still producing ~50% of all small molecules, and in the years 2000 and 2001, a significant number of NCEs were in fact biologicals or vaccines.

Overall, of the 1031 NCEs covering all diseases/countries/sources in the years 1981−2002, 43% were synthetic in

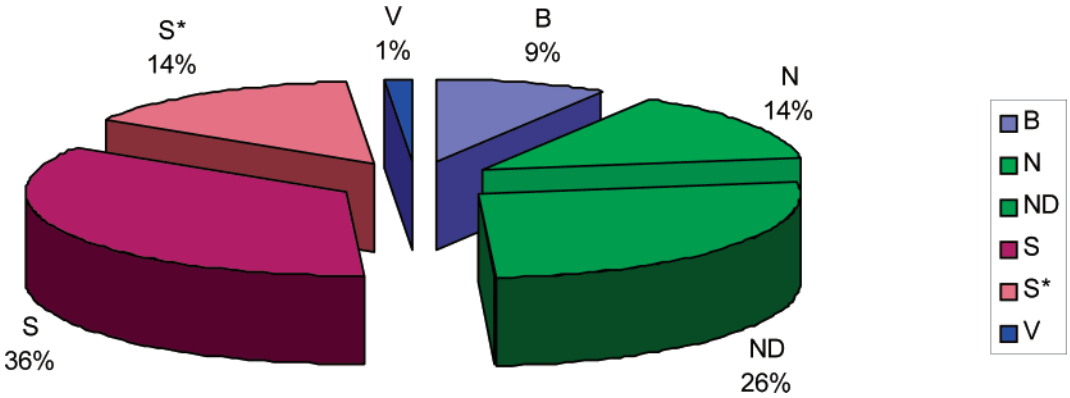


Figure 6. All available anticancer drugs, 1940s−2002, by source without "NM" subdivision ($N = 140$).

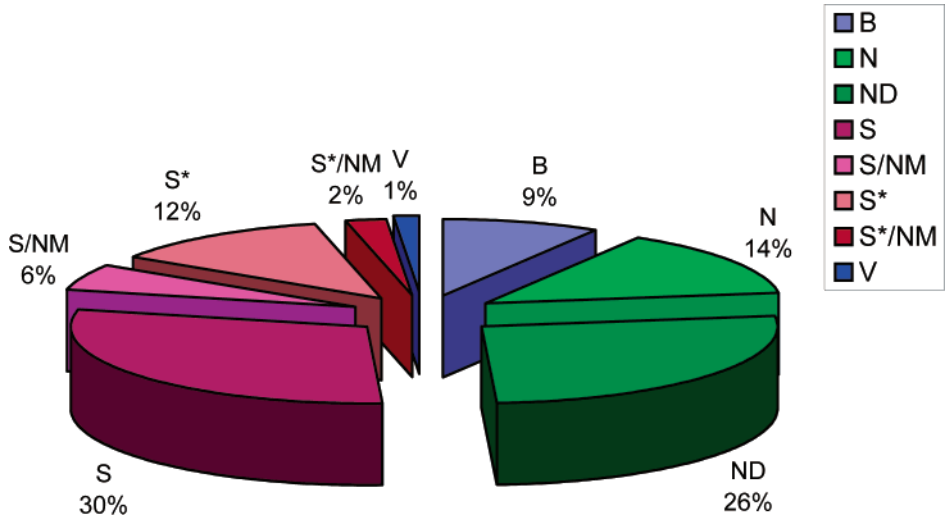


Figure 7. All available anticancer drugs, 1940s−2002, by source with "NM" subdivision ($N = 140$).

Table 9. Antimigraine Drugs from 1981 to 2002 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	reference	page	source
lomerizine hydrochloride	Teranas	1999	ARMC 35	342	S
pirprofen	Rengasil	1982	P091061		S
almotriptan	Almogran	2000	DNP 14	13	S*/NM
eletriptan	Relpax	2001	DNP 15	30	S*/NM
frovatriptan	Frova	2002	P212285		S*/NM
naratriptan hydrochloride	Naramig	1997	ARMC 33	339	S*/NM
rizatriptan benzoate	Maxalt	1998	ARMC 34	330	S*/NM
sumatriptan succinate	Imigran	1991	ARMC 27	333	S*/NM
zomitriptan	Zomig	1997	ARMC 33	345	S*/NM
alpiropride	Rivestel	1988	ARMC 24	296	S/NM

origin, but if one removes the S/NM category from this total, then the S category falls to 33% (Figure 1). Thus, depending upon the subcategories, the gross figures for categories other than synthetic range from 57% to 67% over all diseases.

Inspection of Tables 1 and 2, which differ only in that the "NM" subcategory is in Table 2 (and in both cases, disease indications that have three or less drugs approved in the 22 years have been removed from the analyses), demonstrates that overall, the major disease areas that have been investigated in the pharmaceutical industry in this time frame are infectious diseases, cancer, and antihypertensives and antiinflammatory indications, all with over 50 approved drug therapies.

Table 10. All Antiinfective (antibacterial, fungal, parasitic and viral) Drugs ($N = 159$)

indication	total	N	ND	S	S/NM	S*	S*/NM
antibacterial	90	9	61	19			1
antifungal	23		2	18	3		
antiparasitic	13	2	5	4		2	
antiviral	33		1	7	1	17	7
total	159	11	69	48	4	19	8
percentage	100.0	6.9	43.4	30.2	2.5	12.0	5.0

In fact, if one takes all antiinfectives, the number is quite astounding, with 162 (18.7%) of the total (868 for indications ≥4) falling into this one major human disease area. On further analysis (Table 10) the influence of other than biologicals and synthetics in this disease complex is such that only a little over 30% are synthetic in origin (the total was reduced by 3 to 159, as a result of removing the biologicals), and these synthetic drugs actually tend to be of two basic chemotypes, the azole-based antifungals and the quinolone-based antibacterials, *though even the quinolones can trace their provenance back to large-scale syntheses of chloroquin (an* S* *molecule) and the serendipitous discovery of antibacterial byproducts based on oxoquinolines*.[63] To emphasize the point, in Table 10 we have extracted the relevant data from Tables 1 and 2.

What is also apparent from inspection of the structural types involved in antiinfective therapy, particularly in the antibacterial arena (Table 3), is that there has been a dearth of novel antibacterial pharmacophores in this time frame. Although two apparently novel structural types were approved, one in 1999 (dalfopristin/quinupristin; Synercid) and another in 2000 (linezolid; Zyvox), if one

determines their respective "*structural provenance*", then the first two are derivatives of a very old antibiotic class, the pristinamycins/staphylomycins, whose major usage was/is as animal feed supplements, and the third traces its heritage back to materials first reported by workers at DuPont in the middle 1980s. One should add, however, that Pharmacia did an elegant job of combinatorially modifying the DuPont structures in order to produce linezolid. Even though the base structure of linezolid had not been exposed to bacteria in a clinical setting, within the year after introduction, a number of reports have surfaced in the clinical microbiology literature reporting significant resistance to this drug, a situation that is reminiscent of the early beta-lactams. All of the other antibacterials reported are modifications of existing structural types. The initial promises/premises of *de novo* combinatorial chemistry do not seem to have blossomed in this area of disease as yet, though by using "privileged structures" based on benzopyrans and vancomycins, Nicolaou and co-workers have demonstrated some extremely interesting structural modifications with significant antibiotic activities against methicillin-resistant *Staphylococcus aureus* (MRSA) and also against vancomycin- and Synercid-resistant *Enterococci*.[64,65]

What is of interest from a natural products perspective is that for the first time since the 1970s two modified natural products have been approved very recently for antifungal therapy (Table 4). These are the first such agents for over 20 years, as all other agents in the analysis are either azoles or squalene epoxidase inhibitors of the terbinafin type. These echinocandin/pneumocandin derivatives are the first glucan inhibitors to actually reach the market following a very lengthy gestation period, as the base structure for the echinocandins was first reported in 1974.[66] The importance of natural products in antifungal chemotherapy has been recently reviewed by the Spanish Merck group and should be consulted for further potential chemotypes.[67]

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 may be obtained from the authors in the form of an Excel 2000 spreadsheet and a database file (dbf), which can be used by interested readers.

As we reported in our earlier analysis,[1] there are still significant therapeutic areas where the drugs are totally synthetic at the present time. These include, but are not limited to, antihistamines, diuretics, and hypnotics for indications with four or more approved drugs (cf., Tables 1 and 2). 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", fall into the "S/NM" subcategory.

From inspection of Tables 1−5, the following points can be made in addition to the digest on antiinfectives given in Table 10. In the antibacterial area (Table 3), as found previously, the vast majority of the 90 NCEs are N (9; 10%), ND (61; 68%), or S*/NM (1; 1%), amounting to 71 in total or 79% of the whole, with the remainder (S) being predominately quinolones. In the antifungal area (Table 4), the roles are reversed, with the great majority being S (18; 75%) and S/NM (3; 13%), with the remainder being ND (2; 8%) and B (1; 4%). In the antiviral area (Table 5), the situation is somewhat different, since 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 35 approved agents the relevant figures are B (2; 6%), ND (1; 3%), and S* and S*/NM categories (24; 68%), with the remainder falling into either S (7; 20%) or S/NM (1; 3%).

With anticancer drugs (Table 6), where in the time frame covered (1981−2002) there were 79 NCEs *in toto*, the number of nonbiologicals was 65 (82%). These could be divided as follows: N (9; 11%), ND (21; 27%), S (17; 21%), S/NM (8; 10%), S* (7; 9%), and S*/NM (3; 4%). Thus, only 21% of the total number of anticancer drugs were classifiable, under our criteria, into the S (synthetic) category. Expressed as a proportion of the nonbiologicals, then 48 of 65 (74%) either were natural products, were based thereon, or mimicked them in one form or another.

In our previous paper on this topic, we had not broken out the anticancer agents in the 1983−1994 time frame, but instead, gave an overview of all agents available through 1994. In our present review, we have continued in this manner and have added the older drugs (i.e., pre-1981) to the more current listing in this disease indication, so that an overall analysis can be made.

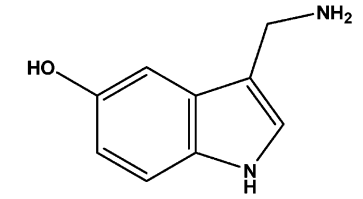
Inspection of Figures 6 and 7 and Table 7 shows that, over the whole category of anticancer drugs effectively available to the West and Japan, the 140 available agents can be categorized as follows: B (12; 9%), N (20; 14%), ND (37; 26%), S (49; 35%), S* (20; 14%), and V (2; 2%), and if the "NM" categories are included, then the relevant figures are S (41; 29%), S/NM (8; 6%), S* (17; 12%), and S*/NM (3; 2%). If one removes the biologicals and vaccines, thus reducing the overall number to 126, the number of nonsynthetic agents (i.e., N, ND, S*) is 77 (62%), and if one now includes the "NM" category, these figures rise to 85 (67%). It should be noted that the 140 agents do not include some of the earlier drugs that were really immuno- or hematologic stimulants, nor etoposide phosphate, which though it is in Table 6 as an approved NCE for the record, is not included in this count, as it is a prodrug of etoposide.

In our earlier paper, the number of nonsynthetic agents was also 62% for other than biologicals, without an "NM" subcategory. Thus the proportion has remained similar despite some reassignments of sources and the expansion of combinatorial chemistry techniques. Further information on the role of natural products in cancer chemotherapy in the past, present, and future is given in the recent review by Mann.[68]

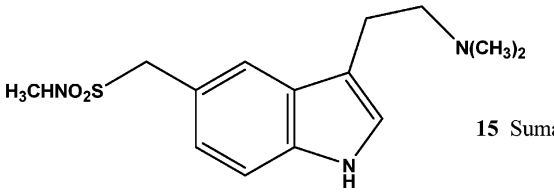
A major general class of drugs that was not commented on in any detail in our original paper[1] is the class that is directed toward the treatment of hypertension. These drugs include diuretics, calcium channel blockers, β-antagonists, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor (AT1R) antagonists. From Tables 1, 2, and specifically Table 8, one can see that, although the great majority of these 75 drugs are synthetic (S) or based upon a natural product pharmacophore (S*), a considerable number of each class may be classified as "NMs". Specifically, one should look at the relative numbers of S (26; 35%) to S/NM (14; 19%) and of S* (2; 3%) to S*/NM (32; 43%). In the former case, the NM category includes the "sartans" or AT1R inhibitors (e.g., structure **11**), and in the latter, the beta-blockers and ACE inhibitors (*vide infra*).

Similarly, if the antimigraine drugs are considered (Table 9), the great majority (7; 70%) are S*/NM and are serotonin uptake/reuptake inhibitors, and inspection of

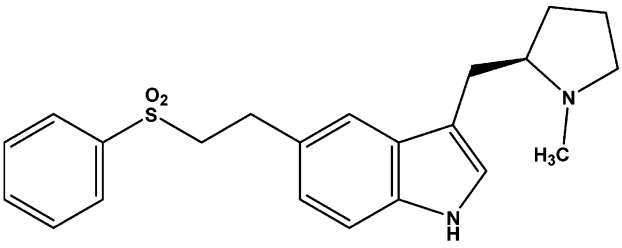
the structures below shows the relationship to 5-hydroxytryptamine (serotonin; **14**), sumatriptan (approved 1991; **15**), and elitriptan (approved 2001; **16**).



14 5-Hydroxytryptamine



15 Sumatriptan



16 Eletriptan

Although not given in any subtable, a very interesting group of compounds classified as other than synthetic have been approved in the years since 1985. Of the 16 anticoagulants approved in the 1981−2002 time frame, the categories are as follows: B (3; 15%), ND (12; 60%), and S* (1; 5%). What is extremely interesting is that 11 of the ND category are based on low molecular weight (chemically degraded) heparins, one is a derivative of hirudin (from leeches), and the sole S* is a short synthetic saccharide that is modeled on the heparin binding site substrate.

Discussion

The decline in the output of the R&D programs of the pharmaceutical companies has been described as a "productivity crisis" by some,[10] and this has been attributed in part to disruption of laboratory activities by the spate of company mergers and acquisitions, the mounting costs of drug development, and FDA overcaution in the drug approval process.[10] Interestingly, no mention is made of the deemphasizing by many companies of the "tried and true" exploration of nature[47] as the source of novel leads for drug development as a possible reason for this downturn.

Though combinatorial chemistry continues to play a major role in the drug development process, it is noteworthy that there is a "growing trend toward the synthesis of complex natural product-like libraries", and adoption of the diversity-oriented synthesis approach where natural product synthesis and combinatorial chemistry are combined.[9] As has been eloquently stated by Danishefsky, "a small collection of smart compounds may be more valuable than a much larger hodgepodge collection mindlessly assembled".[69] This approach has received significant support from the government via an RFP for Centers of Excellence in Chemical Methodologies and Library Development (at http://www.nigms.nih.gov), but unfortunately the major pharmaceutical companies continue to deemphasize their natural products programs. Once again, Danishefsky has provided succinct commentary:

> Thus, the decision on the part of several pharma companies to get out of the natural products business is gross foolishness. There are major teachings in these natural products that we would do well to consider. They may be reflecting eons of wisdom and refinement. The much maligned natural products collections did, after all, bring us to statin, β-lactam, aminoglycoside, and macrolide blockbuster drugs. In fact, one of the most promising approaches in diversity chemistry is to produce diversity-chemistry-derived collections that benefit from or partake of the 'wisdom' of natural products.[69]

In this paper we have demonstrated, *yet again*, that natural products play a dominant role in the discovery of leads for the development of drugs for the treatment of human diseases. Much of nature remains to be explored, particularly the marine and microbial environments, and the interplay of these two sources, as exemplified by the very recent review by Colwell,[70] leaves no doubt that a host of novel, bioactive chemotypes await discovery.[71]

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.

In our earlier paper,[1] we quoted Dr. Dennis Pirages, Director of the Harrison Center on the Future Global Agenda of the University of Maryland, as stating that "infectious diseases are potentially the largest threat to human security lurking in the post cold-war world". With the explosion of the AIDS pandemic, the continuing scourges of malaria and tuberculosis, and the post-September 11, 2001, emergence of threats of mass circulation of highly contagious pathogens by terrorist organizations, the need for expediting the discovery of more effective antiinfective agents is all the more urgent.

Once more, 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.

A file in dbf format containing generic and trade names, source designations, MOA where relevant, and references together with an Excel 2000 workbook giving the statistics derived from the database are available free of charge from the corresponding author via e-mail.

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NP030096L