# *Reviews*

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

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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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**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, $\beta$-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, antiatherosclerotic, 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.

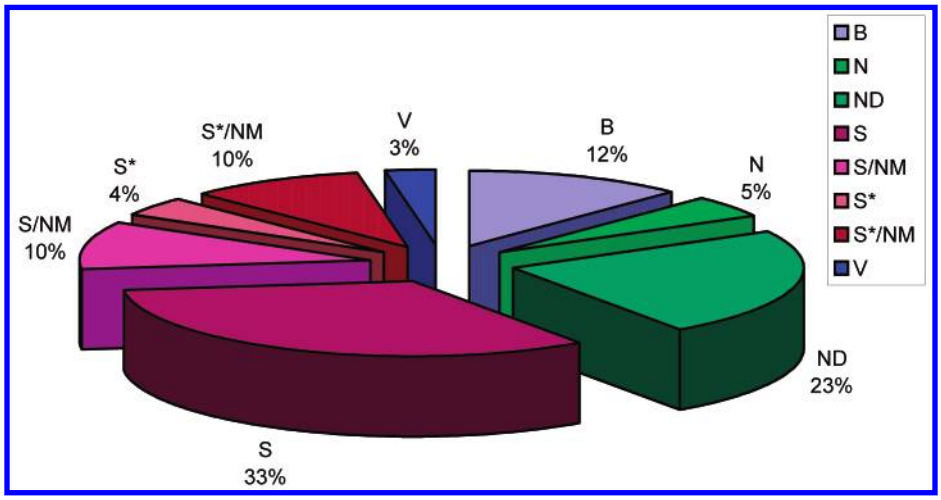



**Figure 1.** All new chemical entities, 1981−2002, by source ($N$ = 1031).

*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 $\beta$-blockers or $\beta$-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]

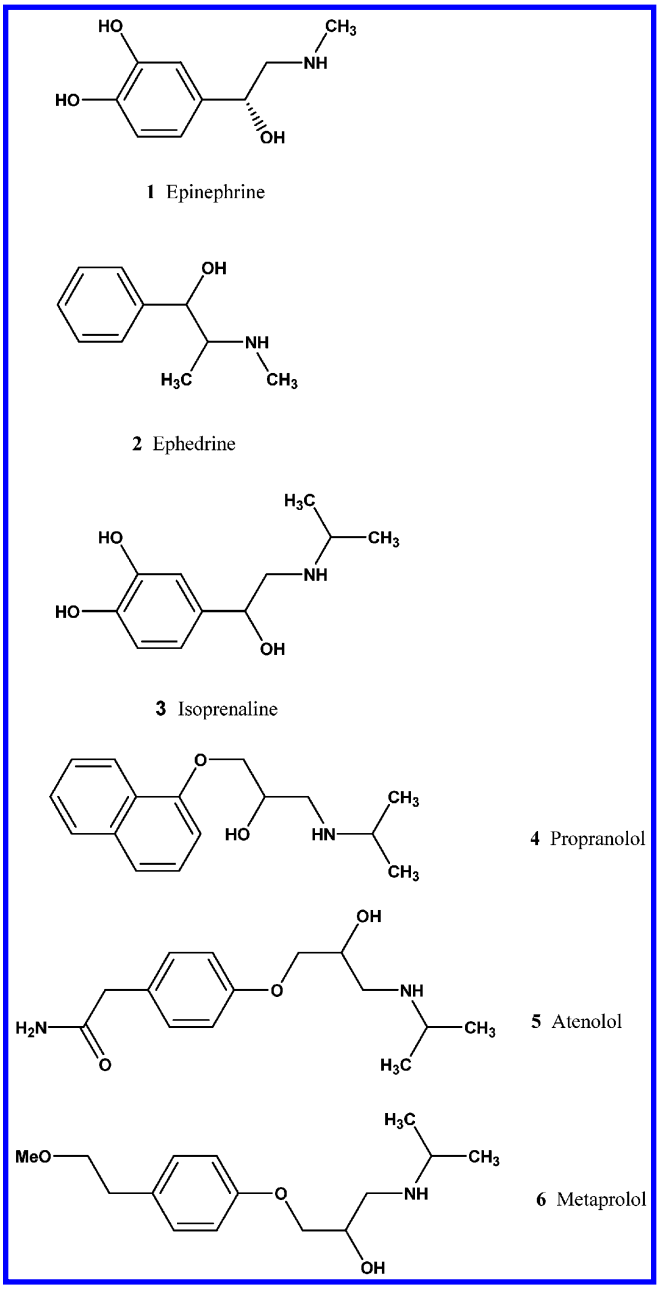
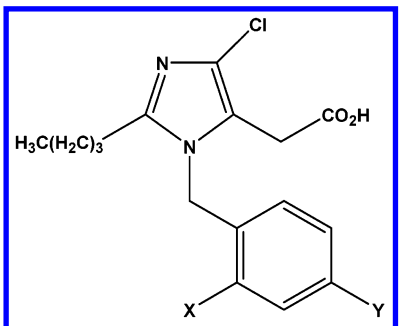


**Table 4.** Antifungal Drugs from 1981 to 2002 Organized Alphabetically by Generic Name within Source

| 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 |

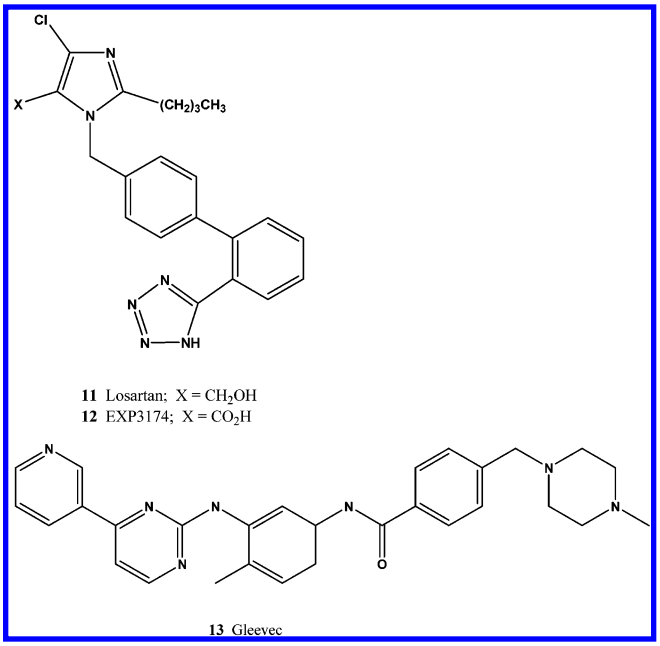
The first lead to a nonpeptidic structure that demonstrated AT1R inhibition was actually from nature. In 1982, workers at Takeda reported in a U.S. patent[53] the structures of three microbial metabolites (structures **7**−**9**) that




**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 $Asp^1$ $\beta$-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.

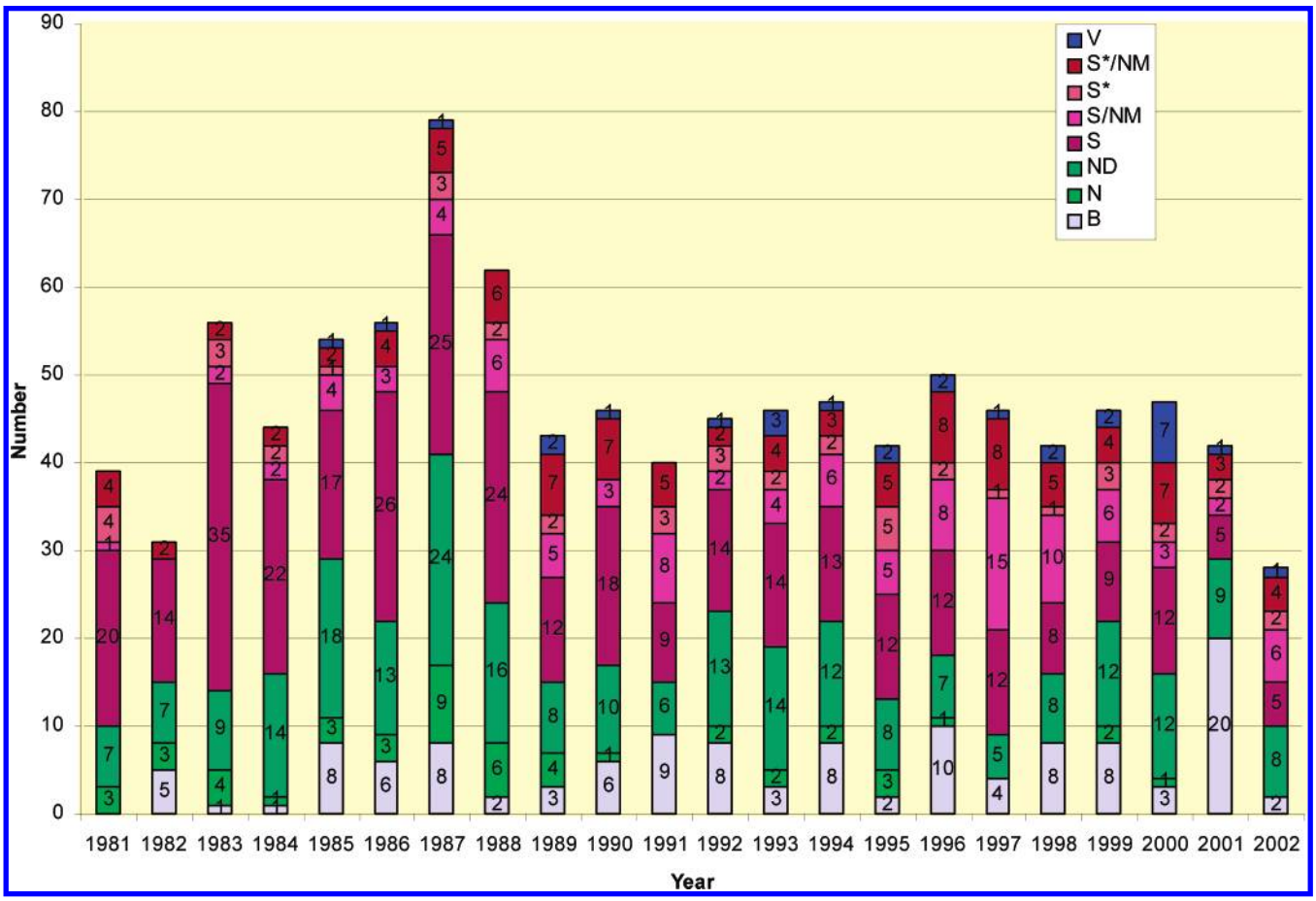



**Figure 2.** All new chemical entities organized by source/year, with "NM" subdivision ($N = 1031$).

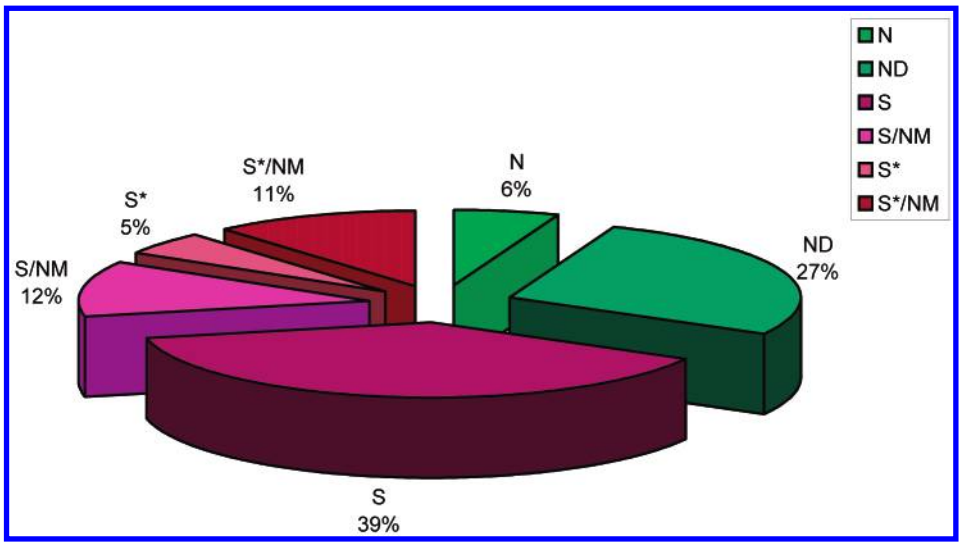



**Figure 3.** All small molecule new chemical entities, 1981−2002, by source with "NM" subdivision ($N = 877$).

- 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 |

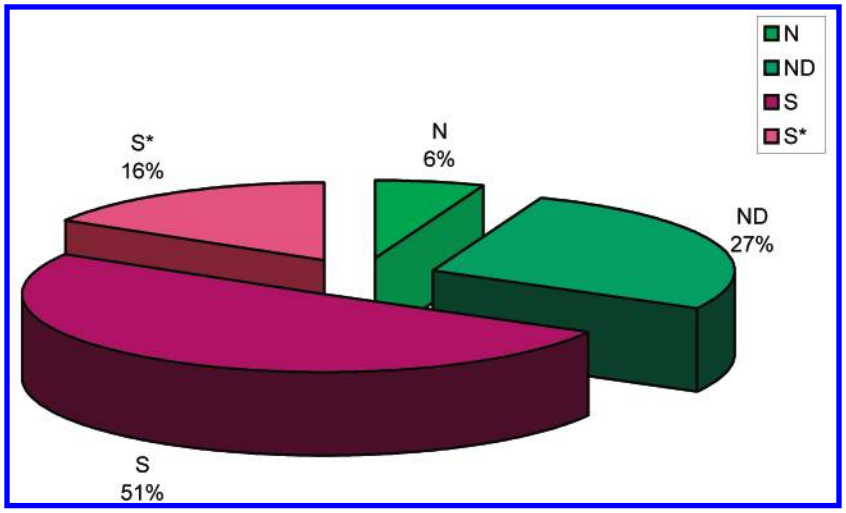



**Figure 4.** All small molecule new chemical entities, 1981−2002, by source without "NM" subdivision ($N$ = 877).

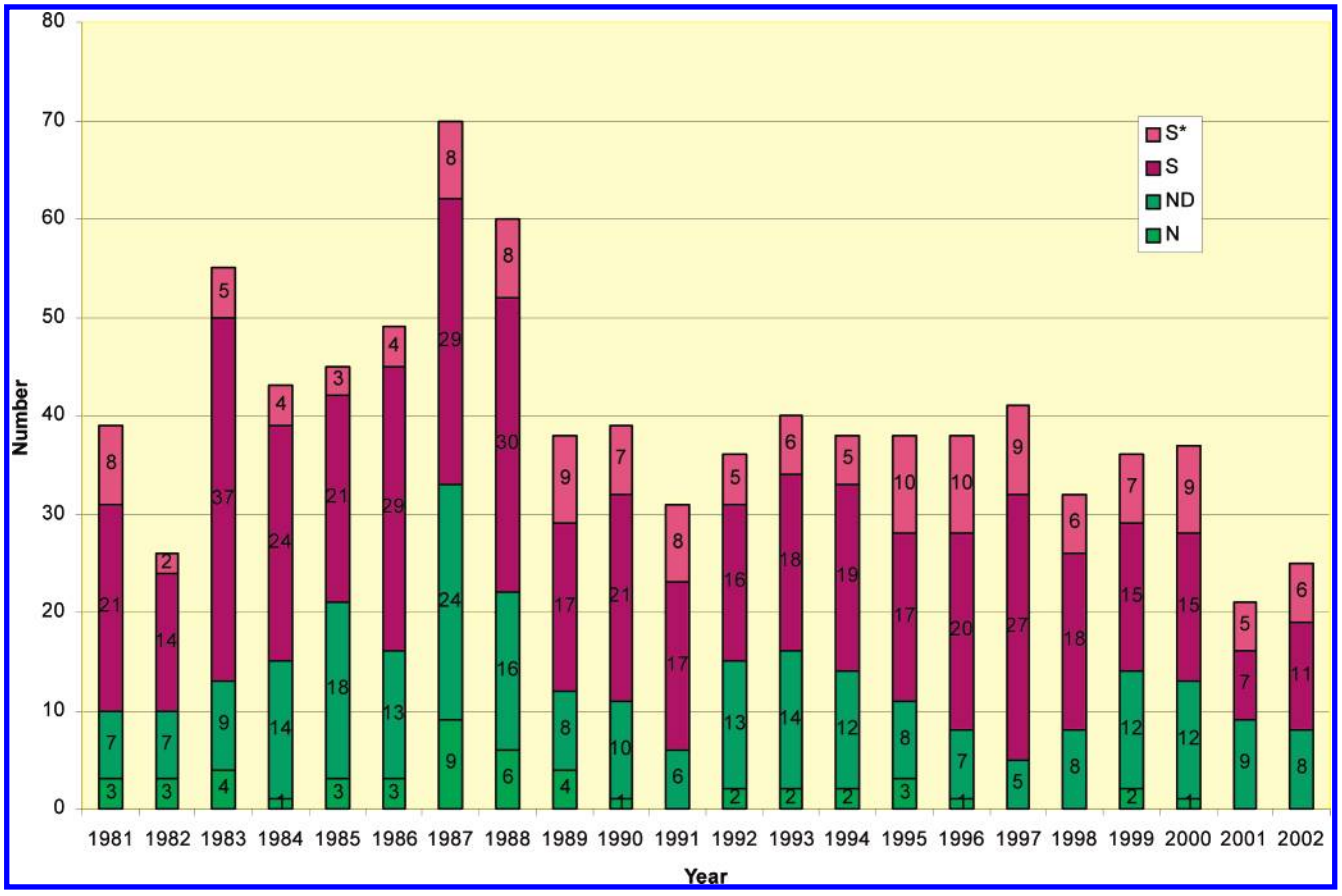



**Figure 5.** Small molecule new chemical entities organized by source/year, without "NM" subdivision ($N$ = 877).

• 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

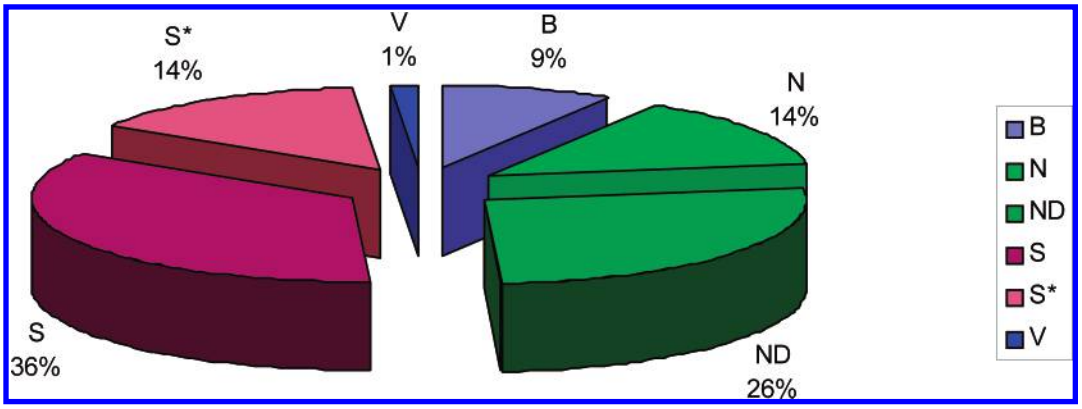



**Figure 6.** All available anticancer drugs, 1940s−2002, by source without "NM" subdivision ($N$ = 140).

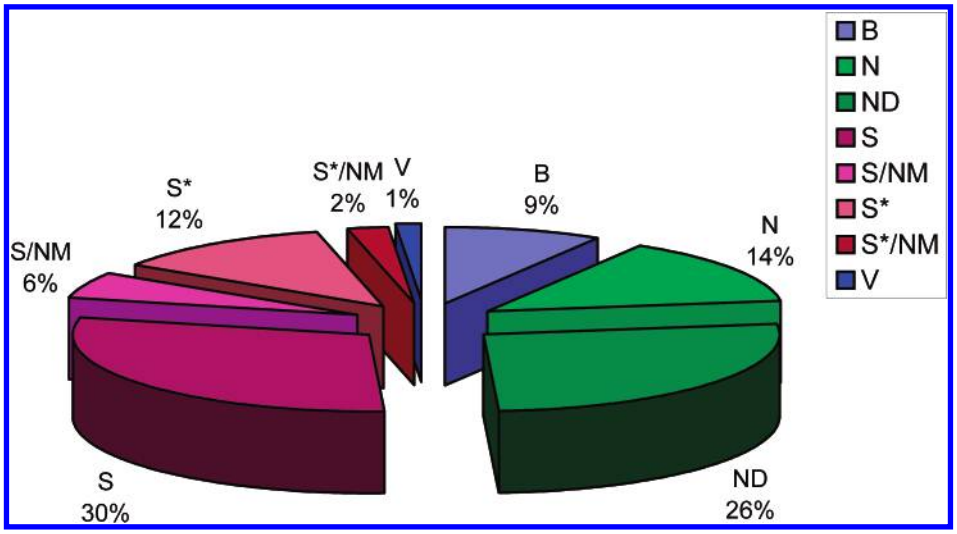



**Figure 7.** All available anticancer drugs, 1940s−2002, by source with "NM" subdivision ($N$ = 140).

**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.

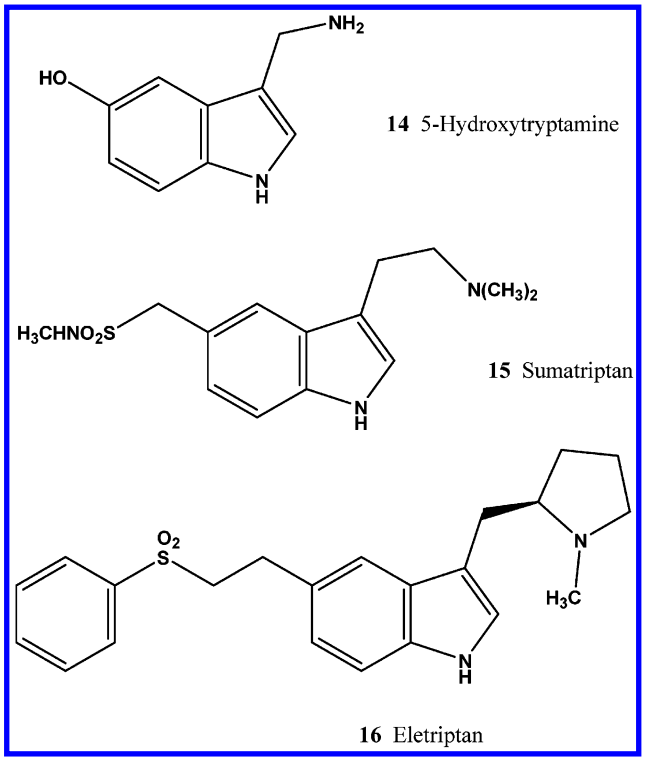
Inspection of Figures 6 and 7 and Table 7 shows that, over the whole category of anticancer drugs effectively available to the West and Japan, the 140 available agents can be categorized as follows: B (12; 9%), N (20; 14%), ND (37; 26%), S (49; 35%), S* (20; 14%), and V (2; 2%), and if the "NM" categories 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, $\beta$-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**).




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, $\beta$-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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