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Review

Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019

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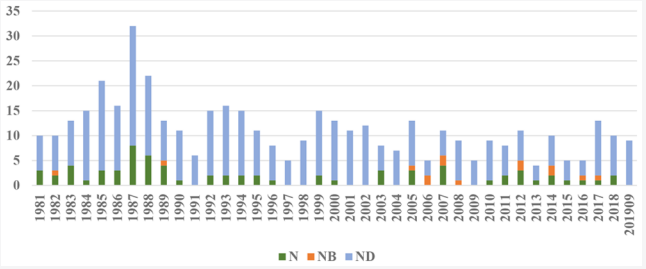
ABSTRACT: This review is an updated and expanded version of the five prior reviews that were published in this journal in 1997, 2003, 2007, 2012, and 2016. For all approved therapeutic agents, the time frame has been extended to cover the almost 39 years from the first of January 1981 to the 30th of September 2019 for all diseases worldwide and from ∼1946 (earliest so far identified) to the 30th of September 2019 for all approved antitumor drugs worldwide. As in earlier reviews, only the first approval of any drug is counted, irrespective of how many "biosimilars" or added approvals were subsequently identified. As in the 2012 and 2016 reviews, we have continued to utilize our secondary subdivision of a "natural product mimic", or "NM", to join the original primary divisions, and the designation "natural product botanical", or "NB", to cover those botanical "defined mixtures" now recognized as drug entities by the FDA (and similar organizations). From the data presented in this review, the utilization of natural products and/or synthetic variations using their novel structures, in order to discover and develop the final drug entity, is still alive and well. For example, in the area of cancer, over the time frame from 1946 to 1980, of the 75 small molecules, 40, or 53.3%, are N or ND. In the 1981 to date time frame the equivalent figures for the N* compounds of the 185 small molecules are 62, or 33.5%, though to these can be added the 58 S* and S*/NMs, bringing the figure to 64.9%. In other areas, the influence of natural product structures is quite marked with, as expected from prior information, the anti-infective area being dependent on natural products and their structures, though as can be seen in the review there are still disease areas (shown in Table 2) for which there are no drugs derived from natural products. Although combinatorial chemistry techniques have succeeded as methods of optimizing structures and have been used very successfully in the optimization of many recently approved agents, we are still able to identify only two de novo combinatorial compounds (one of which is a little speculative) approved as drugs in this 39-year time frame, though there is also one drug that was developed using the "fragment-binding methodology" and approved in 2012. We have also added a discussion of candidate drug entities currently in clinical trials as "warheads" and some very interesting preliminary reports on sources of novel antibiotics from Nature due to the absolute requirement for new agents to combat plasmid-borne resistance genes now in the general populace. We continue to draw the attention of readers to the recognition that a significant number of natural product drugs/leads are actually produced by microbes and/or microbial interactions with the "host from whence it was isolated"; thus we consider that this area of natural product research should be expanded significantly.



INTRODUCTION

It is now close to 23 years since the publication of our first review covering drugs from 1984 to 1995[1] and 17 years since the second that covered the period from 1981 to 2002,[2] 12 years since our third covering the period 1981 to the middle of 2006,[3] seven years since we covered 1981 to 2010,[4] and almost five years since our last full analysis (covering the period 1981 to 2014), which was published in early 2016,[5] of the sources of new and approved drugs for the treatment of human diseases. In this current review, we have covered the almost five years from the first of January 2015 to the 30th of September 2019.

Since the last review, we have also published either together, independently, or with other authors a number of intermediate reports and/or standalone articles on natural products as drug leads or actual drugs. A partial listing includes the following: endophytic and epiphytic microbes as sources of bioactive natural products;[6−8] marine drug candidates;[9] a chemometric analysis of the natural product drugs in the 2016 review versus synthetic drugs;[10] a review of methods of "persuading" microbes to reveal their hidden genetic information;[11] natural product scaffolds of value in drug discovery;[12] a discussion on the value of marine-derived drugs;[13] the influence of nucleosides and adrenergic agents on drug discovery;[14] a discussion on the influence of Brazilian biodiversity on drug

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discovery covering the pederine-based drug candidates and the sources of ACE inhibitors;[14] the screening of natural product extracts to identify complex 1 bypass factors;[15] a review of currently uncultured microbes as sources of natural products;[16] a chapter on biodiversity and drug discovery (in a Brazilian book);[17] a review on marine-derived warheads for antitumor antibody−drug conjugates;[18] a review on current screening methods to identify natural product-based compounds;[19] a book chapter on microbial involvement in natural product production by organisms from all kingdoms;[20] a requested review on bioactive cyclic molecules and drug design;[21] a short discussion article on synthetic modifications of vancomycin structures to overcome resistance;[22] a chapter on natural products as antitumor compounds;[23] a chapter on pharmacological aspects of marine natural products, but not involving any antitumor agents;[24] a discussion piece covering the "true producers" of natural products from microbial sources;[25] a review discussing the use of both large-scale collections and genomic techniques with marine natural products;[26] a chapter on extremophilic marine fungi;[27] and a recent article on marine-derived agents as warheads in ADCs.[28] All these articles demonstrate that natural product and/or natural product structures continued to play a highly significant role in the drug discovery and development process.

In addition, for the benefit of new readers, we have shown in Table 1 the codes that we have used and modified over the years with the dates of the reviews in which we introduced them.

Table 1. Codes Used in Analyses

code	brief definition/year
B	biological macromolecule, 1997
N	unaltered natural product, 1997
NB	botanical drug (defined mixture), 2012
ND	natural product derivative, 1997
S	synthetic drug, 1997
S*	synthetic drug (NP pharmacophore), 1997
V	vaccine, 2003
/NM	mimic of natural product, 2003

That Nature in one guise or another has continued to influence the design of small molecules is shown by inspection of the information given below, where with the advantage of now almost 39 years of data from 1981 to the end of September 2019, the system has been refined in the following ways. We have eliminated some more duplicative entries that crept into the earlier data sets and continued to revise some source designations as newer information was obtained from diverse sources. In particular, as behooves authors originally from the National Cancer Institute (NCI), in the specific case of cancer treatments, we continued to consult the records of the FDA and added comments from investigators who have informed us of compounds that may have been approved in other countries and that were not captured in our earlier searches. As a slight modification from prior reports, we are presenting the cancer data in two time series: agents approved before the beginning of 1981 with the first "date" now being 1946, thus covering the molecules from 1946 to the end of 1980, then antitumor agents approved from 01JAN1981 to 30SEP2019. This avoids duplication in the relevant tables, and we have added a graphic demonstrating the total "sources" of approved antitumor agents from 1946 in the relevant sections later in the review.

A trend mentioned in our 2003 review,[2] namely, the shift away from large combinatorial libraries, has continued today, with the emphasis continuing to be on small focused (100 to ∼3000 plus) collections that contain much of the "structural aspects" of natural products. In previous reviews we described the various names given to these newer processes including "diversity-oriented syntheses". As mentioned in our last (2016) review,[5] we still prefer to simply refer to such compounds as "more natural product-like" in terms of their combinations of heteroatoms and significant numbers of chiral centers within a single molecule as described in 2005 by Reayi and Arya.[29] Another term could be "natural product mimics" if they happen to be direct competitive inhibitors of the natural substrate, which was the origin of our subset listed as ?/NM. Although we have mentioned it before, Lipinski's fifth rule effectively states that the first four rules do not apply to natural products nor to any molecule that is recognized by an active transport system when considering "druggable chemical entities". We will reference those papers in this review that demonstrate this, as even today, many years later, synthetic chemists still do not (or will not?) take this into account.[30−32] We also suggest that, even though it is now seven plus years old, the paper by Koehn in 2012 be "mandated reading for chemists" interested in NP-based drug design. In that article, the list in their Table 1 shows the 26 drugs approved between 1981 and 2011, based on 18 natural product structures, that do not obey the "Rule of 5" and its strictures.[33] Following on from the Koehn article, in 2017, a group at AbbVie published an excellent and relatively short perspective in the *Journal of Medicinal Chemistry* showing the 12 FDA-approved drugs that are orally active and were approved from 2014 to 2016. Six of these drugs were for the treatment of HCV, four were antitumor agents, one was for the treatment of nausea from chemotherapy, and one was for cardiovascular treatment, with molecular weights ranging from 531 to 894 and cLogP values from −0.9 to 10.4. The paper is also worth reading for its discussion of the large number of AbbeVie compounds that are orally active and violate more than one of the Lipinski rules. The paper was online in late 2017 and formally published in 2018.[34] An earlier paper in 2014 by the Khilberg group also demonstrated that bioactive compounds can significantly violate the Lipinski rules and demonstrate oral bioactivity.[35]

Current examples of the use of small focused libraries (with "small" meaning less than 5000 compounds in a related library) are given in four recent papers. These range from the results of a 96-member quinone-based click chemistry library against *Cdc25* phosphatases, demonstrating a potent and selective agent that was active against the vinca alkaloid-resistant cell line KB-vin;[36] the use of a peptide array synthesis based upon a microfluidic printing system from which 625 tetrapeptides were screened against the $\alpha 4\beta 1$ integrin system identifying Arg-Ala and Ala-Asp constructs that did not bind to Jurket cells, thus demonstrating both the technique and discovery of potential structures with the desired activities;[37] and the use of the Waldmann BIOS system to discover a simplified structure derived from an indole alkaloid-like skeleton that inhibited the *crm-1/NPM1* locus (structures **1**, **2**).[38] Then, very recently an extension of methodologies has demonstrated how compound libraries from (some) privileged structures can lead to compounds that would have been marked by the PAINS filters first established in the 2010 time

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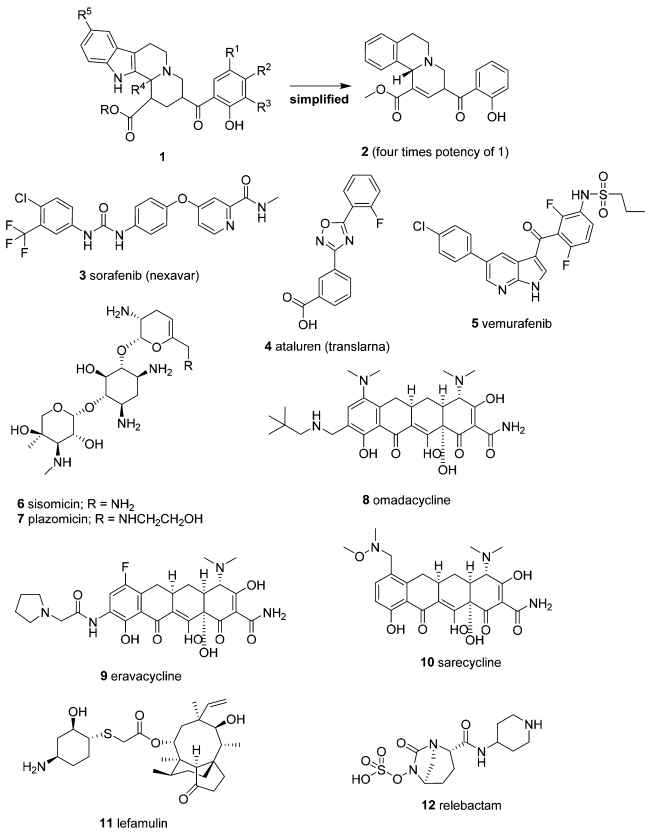
frame and discussed in conjunction with the IMPs compounds in our 2016 review; these newly identified compounds now have utility as probes even though they would be marked by the PAINS filters.[39] Thus, one needs to be careful in rejecting compounds via automated processes. The IMPs and PAINS compounds referred to above were further discussed in a comprehensive though short paper in *PLOS Pathogens* in 2018 by Plemper and Cox, where they pointed out the large number of papers in the scientific literature that had given totally false impressions of the "value" of most of these compounds as viable leads to new drug entities, mainly from initial high-throughput screens.[40] This article contains interesting statistics on publications covering resveratrol and curcumin as false leads, thus demonstrating the value of the two review articles warning of the problems.

Even though combinatorial chemistry has now been used in one way or another as a discovery source for over 90% of the time covered by this review, to date, we still can find only three approved new chemical entities (NCEs) reported in the public domain: the antitumor compound known as sorafenib (Nexavar, **3**) from Bayer, originally approved by the FDA in 2005 for treatment of renal cell carcinoma; ataluren (Translarna; **4**),[41] which was approved in the EU in 2014; and, third (though not in chronological sequence), vemurafenib (**5**), approved by the FDA in 2011, which could be described as using a variation on "combichem". This was the first (anticancer) drug constructed by use of fragment screening and model fitting,



To date we cannot find other examples, but as emphasized by the current authors, and a significant number of other authors in prior reviews on this topic, the developmental capability of combinatorial chemistry as a means for structural optimization, *once an active skeleton has been identified, is without par*. Two recent reviews, one in 2017[42] and the other in 2018,[43] aptly demonstrate what can be achieved using bioactive compound collections and identifying their targets usually via phenotypic screening. However, as found in our 2016 review, which covered up to the end of 2014, although the numbers of approved drugs from worldwide sources (not simply the U.S. FDA, an error frequently made by authors when referencing our reviews) have moved upward, with figures ranging from 48 (for January through September of 2019) to 75 in 2018, a significant number fell into the "B" and "V" categories in those four and three-quarter years. The numbers in the "B" category would have been substantially higher, but we deliberately did not count any approvals of "biosimilars", defined as a biological agent that was effectively identical to an earlier approved drug entity, in any country during this time frame, nor as done previously, did we count any approval aside from the first one irrespective of country/disease.

RESULTS

As in our earlier reviews,[1−5] the data have been analyzed in terms of numbers and classified according to their origin using the previous major categories and their subdivisions.

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

"B": Biological; usually a large (>50 residues) peptide or protein either isolated from an organism/cell line or produced by biotechnological means in a surrogate host
"N": Natural product
"NB": Natural product "Botanical" (in general these have been recently approved)
"ND": Derived from a natural product and is usually a semisynthetic modification
"S": Totally synthetic drug, often found by random screening/modification of an existing agent
"S*": Made by total synthesis, but the pharmacophore is/was from a natural product
"V": Vaccine

Subcategory.

"NM": Natural product mimic (see rationale and examples below as they give the reasoning for the "S" and "S*" categories from the 2003 review onward)

Rationale for "/NM" Subcategory. In the field of anticancer therapy, the advent in 2001 of Gleevec, a protein tyrosine kinase inhibitor, was justly heralded as a breakthrough in the treatment of leukemia. This compound was classified as an "/NM" on the basis of its competitive displacement of the natural substrate, ATP, in which the intracellular concentrations can approach 1−5 mM. As in the 2016 and earlier reviews, we continued to classify most kinase inhibitors (irrespective of whether they are directed against tyrosine or serine/threonine kinases) that are approved as drugs under the "S*/NM" category for exactly the same reasons originally elaborated in the 2003 review.[2] As recognized and discussed reasonably thoroughly in the 2016 review, a number of later kinase inhibitors are not competitive inhibitors of ATP and thus are not classified this way. In addition to the excellent 2015 paper by Fabbro et al.,[44] pointing out that kinase inhibitors are not only for cancer treatment, as these enzymes occur in many different areas of the body, one should also consult a more recent but similar discussion in the 2018 review by Ferguson and Gray that aptly expands on Fabbro's papers

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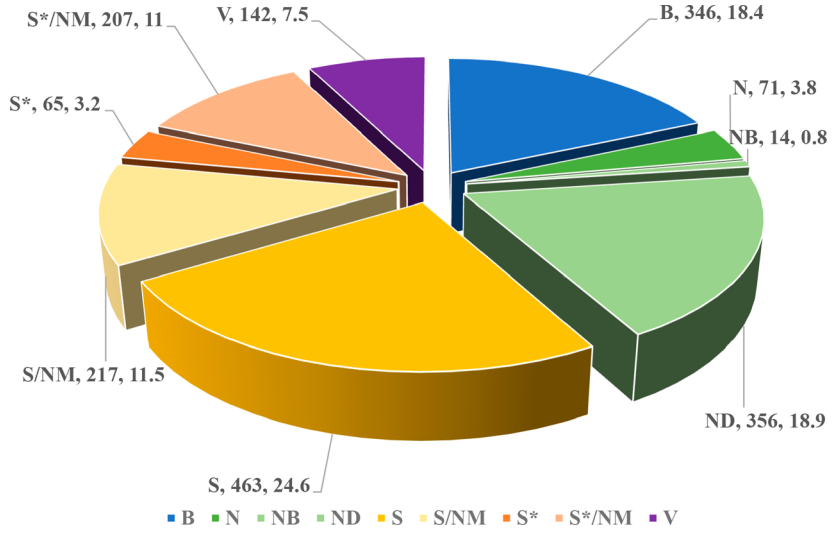

Figure 1. All new approved drugs 01JAN81 to 30SEP19; n = 1881.

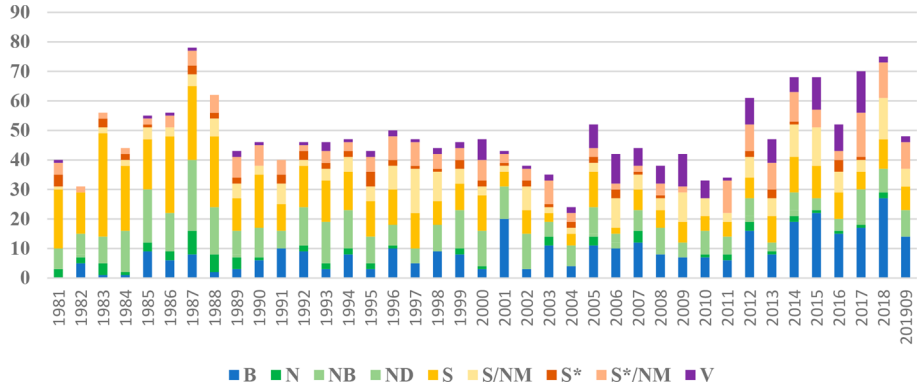

Figure 2. All new approved drugs by source/year; n = 1881.

and shows just how ubiquitous these processes are in both healthy and diseased tissues.[45]

As previously, we have continued to extend the "/SM" category to cover other direct inhibitors/antagonists of the natural substrate/receptor interaction whether obtained by direct experiment or by in silico studies followed by direct assay in the relevant system.

Similarly, a number of old and new peptidic drug entities, although formally synthetic in nature, are simply produced by synthetic methods rather than by the use of fermentation or extraction. In some cases, an end group might have been changed for ease of recovery. However, a number of compounds produced totally by synthesis are in fact isosteres of the peptidic substrate and are thus "natural product mimics" in the truest sense of the term.

Finally, a review covering the preparation of biologically active peptides was published in 2014 and makes interesting reading when the methodologies are compared with those covering the synthesis of pseudopeptides that inhibit aspartic proteinases.[46]

Modification of Natural Products by Combinatorial Techniques. Modifications of natural products by combinatorial methods, not, we hasten to add, the de novo use of combichem, but the expansion/modification of natural product structures, producing entirely different compounds that may bear little if any resemblance to the original, are legitimately assignable to the "/NM" category. In addition to the citations given in our previous reviews, there are some recent review articles that can be consulted that demonstrate how "privileged structures from Nature" are sources of molecular skeletons around which one may build libraries. These are well described by Kumar and Waldmann,[47] and a "hunt for an optimization of peptide macrocycles" is well described by White and Craik.[48] In addition, the 2018 discussion by Chen et al. on the chemical space occupied by natural products[49] is also highly relevant.

Overview of Results. The time frame covered is now the $38^{3}/_{4}$ years from 01JAN1981 to 30SEP2019. The data are cumulative from our earlier reviews, with removal of some duplicates and the use of a single term in most cases for a disease. For example, diabetes is now condensed into one term rather than using type designations. The data on the 1881 approved drug entities since the beginning of 1981 that we have been able to identify have been analyzed and presented in a variety of ways including bar graphs and pie and radar charts, together with major and minor tables that are specific to a given disease moiety

Long-term readers may note that we have removed one of the cumulative tables used in prior reviews: the table that showed all antitumor drugs from the late 1930s to the last date used in a specific review. The reason is that the table is duplicative, so it has been replaced with the following: a table showing the specifics from 1946 to 1980; a corresponding graphic; and a bar graph using the cumulative data from 1946 to 30SEP2019. We moved the date of the first usage of

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materials based on what are now known as "nitrogen mustards" to 1946, as there are significant reports of clinical trials in the USA around that time, though the month is not given. Thus, readers can now choose their data sets from the two tables and graphics as they desire.

The following is a listing of the tables/figures so that readers can consult whichever diseases are of import to them. We have introduced the "radar plot" graphic in some of the following, as it shows the start of a particular class of agents, particularly the introduction of approved biologicals and their corresponding dates/diseases.

- Codes used in analyses (Table 1)
- New approved drugs: from all source categories; pie chart (Figure 1)
- New approved drugs: by source/year; bar graph (Figure 2)
- All approved drugs by year; radar plot (Figure 3)

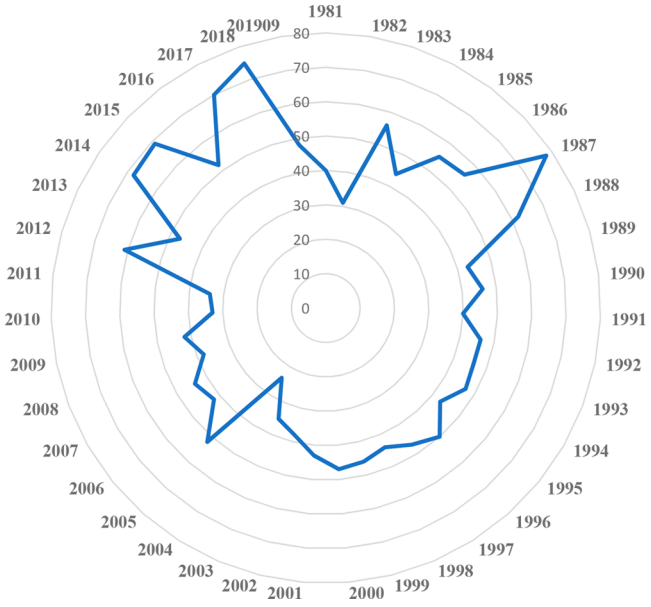

Figure 3. Radar plot of all approved drugs by year; n = 1881.

- All approved biologicals by year; radar plot (Figure 4)
- Sources of small-molecule NCEs: all subdivisions; pie chart (Figure 5)
- Sources of small-molecule NCEs; by source/year; bar graph (Figure 6)
- Total small molecules; by year; radar plot (Figure 7)
- Percentage of N* sources: by year; bar graph (Figure 8)
- N/NB/ND & S* categories: by year; bar graph (Figure 9)
- New chemical entities and medical indications by source of compound (where four or more drugs were approved per medical indication. and listings of diseases with ≤3 approved drugs) (Table 2); these two sets were kept together so that readers can easily see which diseases have low numbers of current drug entities available for treatment
- Disease indications/sources by number of approved drugs; bar chart (Figure 10)
- Antibacterial drugs: generic and trade names, year, reference, and source (Table 3)

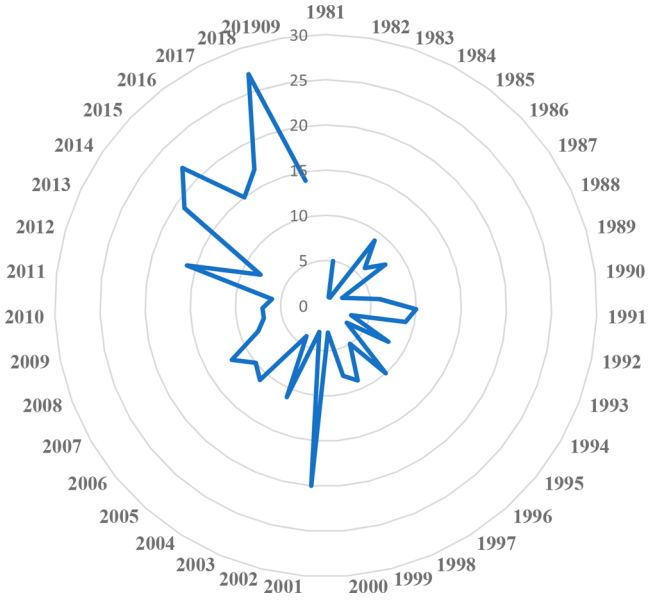

Figure 4. Radar plot of all approved biologicals by year; n = 346.

- Antibacterial drugs: all subdivisions; pie chart (Figure 11)
- Antifungal drugs: generic and trade names, year, reference, and source (Table 4)
- Antifungal drugs: all subdivisions; pie chart (Figure 12)
- Antiviral drugs: generic and trade names, year, reference, and source (Table 5)
- Antiviral drugs: all subdivisions; pie chart (Figure 13)
- Antiparasitic drugs: generic and trade names, year, reference, and source (Table 6)
- Antiparasitic drugs: all subdivisions; pie chart (Figure 14)
- All anti-infective drugs: sources, numbers, and percentages (Table 7)
- Anticancer drugs (01JAN1981−30SEP2019): generic and trade names, year, and reference by source (Table 8)
- Anticancer drugs (01JAN1981−30SEP2019): all drugs pie chart (Figure 15)
- Anticancer drugs (01JAN1981−30SEP2019); all drugs bar graph (Figure 16)
- Anticancer drugs (01JAN1981−30SEP2019); small molecules pie chart (Figure 17)
- Anticancer drugs (01JAN1981−30SEP2019); small molecules bar graph (Figure 18)
- Anticancer drugs: from 1946 to 1980; generic names, year, and reference by source (Table 9)
- Anticancer drugs from 1946 to 1980; pie chart (Figure 19)
- Anticancer drugs from 1946 to 1980; bar graph (Figure 20)
- Anticancer drugs from 1946 to 30SEP2019; all sources, cumulative bar chart (Figure 21)
- Antidiabetic drugs: generic and trade names, year, reference, and source (Table 10)
- Antidiabetic drugs; pie chart (Figure 22)
- Multiple sclerosis agents: generic and trade names, year, reference, and source (Table 11)
- Multiple sclerosis agents; pie chart (Figure 23)

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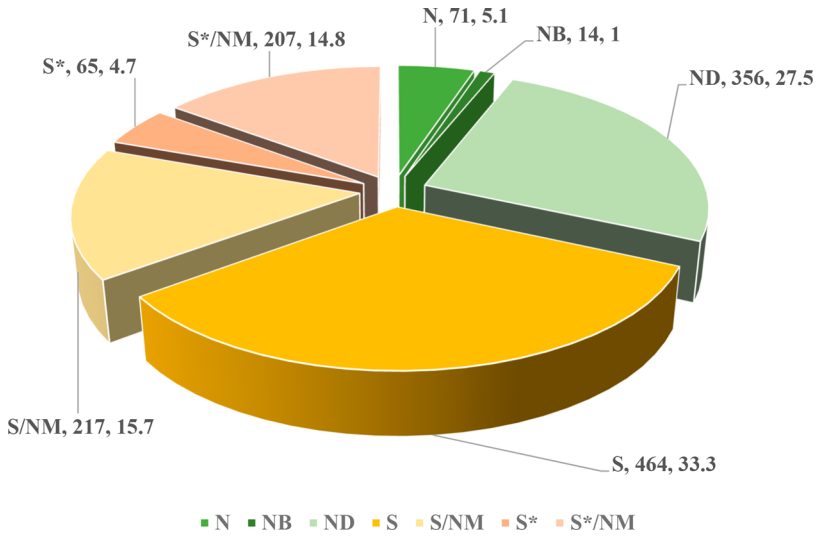

Figure 5. All small-molecule approved drugs 01JAN81 to 30SEP19; *n* = 1394.

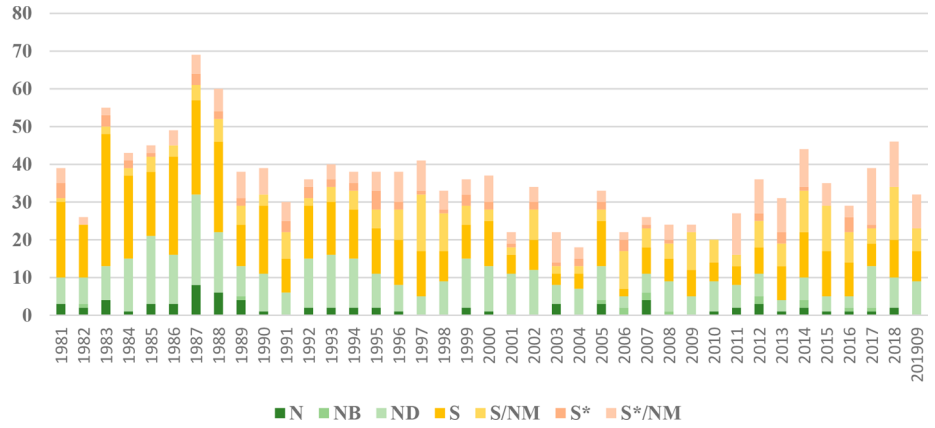

Figure 6. Small-molecule approved drugs 01JAN81 to 30SEP19; *n* = 1394 (bar graph).

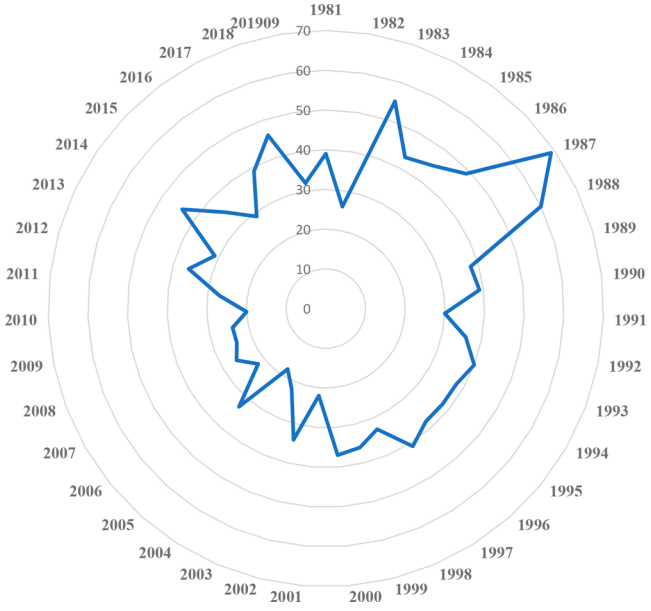

Figure 7. Small-molecule approved drugs 01JAN81 to 30SEP19, *n* = 1394 (radar plot).

- Antiglaucoma agents: generic and trade names, year, reference, and source (Table 12)
- Antiglaucoma agents; pie chart (Figure 24)
- Antibody drug conjugates in phase II and III clinical trials as of 27DEC19 (Table 13)

The extensive data sets shown in the figures and tables referred to above continue to highlight the continuing role that natural products from all sources, structures derived from them, or a "pharmacophore" that is from a natural product have played, and continue to play, in the development of the current therapeutic armamentarium of the physician. Inspection of the data continues to show the important role for natural products in spite of the greatly reduced level of natural products-based drug discovery programs in major pharmaceutical houses.

The disease areas listed above will be discussed, with the majority of the comments being on approvals in the last (almost) 5 years, the period covered since our last review, though at times, we will go into the past as well in order to discuss specific points in the cases of the multiple sclerosis (MS) and antidiabetic drugs.

We will also make comments at the end of the review, in the case of antibody−drug conjugates, on agents that are in phase II and III clinical trials that fall into the N* categories when (and we are being a trifle optimistic) they are approved in the

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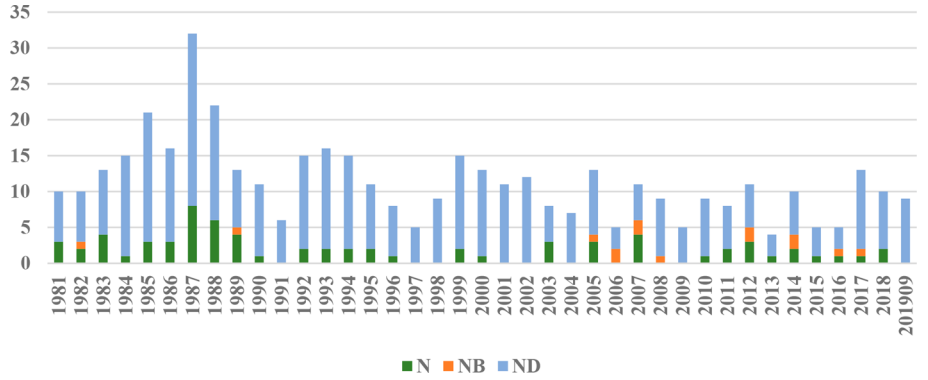

Figure 8. Percentage N* by year 01JAN81 to 30SEP19, mean/SD 32 ± 9%.

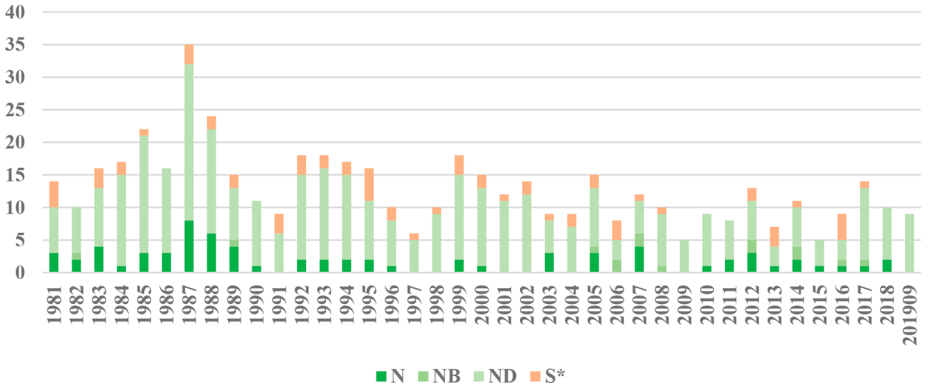

Figure 9. N/NB/ND & S* categories 01JAN81 to 30SEP19, n = 506.

not too far distant future. We will also comment on the problems with anti-infective agents, particularly antibacterials, highlighting two novel natural products that have been reported from the same academic group. Readers can appreciate that not all disease areas will have the same amount of detailed discussion; otherwise, this review would turn into a book.

Discussion of the Overall Results. We have shown the breakout of all 1881 approved agents during the time frame from the beginning of 1981 as a pie chart in Figure 1 and as a bar chart in Figure 2.

We have also added two new figures to this introduction utilizing a format known as a radar plot, as these demonstrate, particularly in Figure 4, the influence of biologics approvals compared to all approvals (Figure 3) in terms of number of molecules approved.

Against this updated backdrop, we now present our analysis of the role of natural products in the drug discovery and development process, dating from 01/1981 through 09/2019. As in our earlier analyses,[1−5] we have consulted the following published sources: *Annual Reports of Medicinal Chemistry* from 1984 to 2014[50−80] and its successor, *Medicinal Chemistry Reviews*, now published as a PDF file.[81−84] Then, in order to obtain more comprehensive coverage of the 1990−2018 time frame, we have added data from the publication *Drug News and Perspective*[85−105] and continued with the successor listings in *Drugs of Today*.[106−114] These, together with searches of the Clarivate *Integrity* database, and inclusion of information from individual investigators form the basis of our data sets. We have continued our attempts to capture vaccine data for the years covered, but this area of the database is still not as complete as we would hope. We have provided a PDF file covering the names, disease(s), year, and codes for the 1881 identified drugs in the 1981−2019 time frame in the Supporting Information.

We have continued to include relevant references in a condensed form in tables where they are relevant (Tables 3 to 6; 8 to 12). If we had attempted to provide full citations, the numbers of references cited in the present review would become overwhelming. In these tables, "ARMC ##" refers to the volume of *Annual Reports in Medicinal Chemistry* together with the page on which the structure(s) and commentary can be found. From 2015, this yearly publication became *Medicinal Chemistry Reviews* commencing with Volume 50 covering drug approvals from 2014 (though it was not used in our last review due to timing constraints), so the corresponding abbreviation is "MCR##". Similarly, "DNP ##" refers to the volume of *Drug News and Perspective* and the corresponding page(s), although this journal ceased publication as of the 2010 volume. In a similar fashion, "DT##" refers to the relevant volume of *Drugs of Today* and the corresponding page(s), and an "I#######" is the accession number in the Prous (then Thomson-Reuters, and now Clarivate) *Integrity* database. Finally, in the overall listing of antitumor agents from 1946 (first confirmed date) through 1980 (Table 9) we have used "Boyd" to refer to a review article[115] on clinical antitumor agents, two earlier books on the same subject, one by Cole[116] listed as "pre-1970 Cole" and Carter[117] listed as "pre-1977 Carter", and the relevant pages in *Martindale's Complete Drug Reference*, 36th edition, as "M'dale".[118] In addition to these references, "FDA" refers to their drugs database and "Japan Antibiotics" to personal communications from Japanese sources. We should emphasize that no duplication has occurred in these tables and their

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Table 2. New Chemical Entities and Medical Indication by Source of Compound 01JAN 81−30SEP19[a]

indication	total	B	N	NB	ND	S	S/NM	S*	S*/NM	V
Alzheimer's disease	6	1	1		1		3			
COPD	11	2					3		6	
Gaucher's disease	5	3			1				1	
PAH	4						3		1	
Parkinson's disease	14				1	1	6	1	5	
allergic rhinitis	5			1						4
analgesic	19		1		2	11	3	2		
anemia (1 sickle cell)	5	1		1		2			1	
anesthetic	5					5				
antiallergic	18		1	1	4	12				
antianginal	5					5				
antiarrythmic	17		1			14			2	
antiarthritic	28	8	1	1	4	4	6		4	
antiasthmatic	15	2			3	2	6		2	
antibacterial	162	4	11		78	36			1	32
anticancer	247	52	18	1	43	29	36	13	45	10
anticoagulant	23	5	13				1	1	3	
antidepressant	28				1	8	17		2	
antidiabetic	63	24	1		8	4	16	1	9	
antidote	6	4			1		1			
antiemetic	11					1	2		8	
antiepileptic	20		1		2	11		3	3	
antifungal	34	1			3	27	3			
antiglaucoma	19	1			6	2	6	1	3	
antihistamine	14					14				
antihyperprolactinemia	4				4					
antihypertensive	82		1		2	28	16	2	33	
antiinflamatory	53	1			13	38	1			
antimigraine	13	3				2	1		7	
antinarcolepsy	5				1	2	1		1	
antiobesity	6				1	1	4			
antiparasitic	20		2		7	6		3		2
antipsoriatic	21	12		1	3	1	2	1	1	
antipsychotic	12					4	6		2	
antithrombotic	30	13	1		5	2	6		3	
antiulcer	36	1	1		12	22				
antiviral	186	17			6	19	9	26	21	87
anxiolytic	10					8	2			
benign prostatic hypertrophy	4			1	1	1	1			
bronchodilator	8				2				6	
calcium metabolism	20				8	9	3			
cardiotonic	13				3	2	3		5	
chelator	4					4				
contraception	11				10		1			
cystic fibrosis	5	1				4				
diuretic	6					4	2			
erythropoiesis	5	5								
gastroprokinetic	4					1	2		1	
hematopoiesis	7	7								
hemophilia	27	27								
hemostatic	5	5								
hormone	22	12			10					
hormone replacement therapy	8				8					
hypercholesterolemia	4	3				1				
hyperphosphatemia	5					5				
hypnotic	12					12				
hypocholesterolemic	14		4		1	2	1		6	
hypolipidemic	8		1			7				
idiopathic thrombocytopenia	7	3				1	2		1	
immunomodulator	6	3	1		1	1				
immunostimulant	14	8	3		2	1				

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Table 2. continued

indication	total	B	N	NB	ND	S	S/NM	S*	S*/NM	V
immunosuppressant	14	6	5		3					
infertility (female)	4	4								
irritable bowel syndrome	8				2	2			4	
macular degeneration	6	4			1	1				
male sexual dysfunction	5								5	
multiple sclerosis	13	5			4	2		1	1	
muscle relaxant	10				4	2	1	3		
neuroleptic	9					1	6		2	
nootropic	8				3	5				
osteoporosis	8	4			3	1				
platelet aggregation. inhibitor.	4				3		1			
respiratory distress syndrome	7	4	1			1	1			
schizophrenia	4						4			
urinary incontinence	7					2	4		1	
vasodilator	5				3	2				
vulnerary	10	6		1	2	1				
total	1602	262	69	8	286	396	192	58	196	135

[a]Diseases where ≤3 drugs approved 1981−09/2019: 279 drugs fall into this category and are subdivided as follows: B, 84; N, 2; NB, 6; ND, 70; S, 67, S/NM. 25; S*, 7; S*/NM, 11; V, 7. These drugs cover the following indications;: 5α-reductase inhibitor, ADHD, Buerger's disease, CAPS, CHF, CLN2, CNS stimulant, CTEPH, Castleman's disease, Crohn's disease, Cushing's syndrome, Duchenne muscular dystrophy, Fabry's disease, GERD, GH deficit, Hunter syndrome, inborn errors of bile synthesis, inflammatory bowel disease, Japanese encephalitis, Lambert-Eaton myasthenic syndrome, Lyme disease, acute MI, MMRC, Morquio A syndrome, PAH, PCP/toxoplasmosis, PNH, Pompe's disease, Turner syndrome, urea cycle disorders, X-linked hypophosphatemia, abortifacient, acromelagy, adenosine deaminase activity, alcohol deterrent, alpha-mannosidosis, amyloidosis, anabolic metabolism, anal fistula, anorexia, antismoking, antiacne, antiatherosclerotic, anticirrhotic, anticonvulsant, antidiarrheal, antiemphysemic, antihyperuricemia, antihypotensive, antinarcotic, antinauseant, antiperistaltic, antiprogestogenic, antirabies, antirheumatic, antisecretory, antisepsis, antiseptic, antispasmodic, antispastic, antitussive, antityrosinaemia, antixerostomia, atrial fibrillation, benzodiazepine antagonist, β-lactamase inhibitor, blepharospasm, bone disorders, bone morphogenesis, bowel evacuant, cancer adjuvant/colorectal, cardioprotective, cardiovascular disease, cartilage disorders, cervical dystonia, choleretic, chronic idiopathic constipation, chronic kidney disease, chylomicronemia syndrome, cognition enhancer, congestive heart failure, constipation, coronary artery disease, cystinosis, cytoprotective, dermatological disorders, diabetic foot ulcers, diabetic neuropathies, disc fusion, disc herniation, disseminated intravascular coagulation, dry eye syndrome, dyslipidemia, dyspareunia, dyspepsia, dysuria, endometriosis, enzyme, expectorant, eye disorders, factor X deficiency, familial amyloid neuropathy, female sexual dysfunction, fertility inducer, free-running circadian disorder, gastroprotectant, genital warts, gout, hematological, hematophagocytic lymphohistiocytosis, hepatoprotectant, hyperammonemia, hyperhydrosis, hyperkalemia, hyperparathyroidism, hyperphenylalaninemia, hypertriglyceridemia, hyperuricemia, hypoammonuric, hypocalciuric, hypogonadism, hyponatremia, idiopathic pulmonary fibrosis, immediate allergy, immunological diseases, joint lubricant, limbal stem cell deficiency, lipodystrophy, lipoprotein disorders, lipoprotein lipase deficiency, lupus erythematosus, lysosomal acid lipase deficiency, mucolytic, mucopoly saccharidosis, mucositis, myelodysplasia, nasal decongestant, neurological disorders, neuropathic pain, neuroprotective, neutropenia, ocular inflammation, opiate detoxification, opiod-induced constipation, osteoarthritis, overactive bladder, ovulation, pancreatic disorders, pancreatitis, paroxysmal nocturnal hemoglobinuria, pertussis, phenylketonuria, photosensitizer, phototoxicity in adults, pituitary disorders, polycythemia vera, porphyria, premature birth, premature ejaculation, progestogen, psychostimulant, purpura fulminans, rattlesnake antivenom, reproduction, restenosis, retinitis pigmentosa, sclerosant, secondary hyperthyroidism, sedative, short bowel syndrome, skin photodamage, sly syndrome, smoking cessation, spinal muscular atrophy, strabismus, subarachnoid hemorrhage, tardive dyskinesia, thalassemia, topical ulcers, treatment of GH deficiency, ulcer treatment, ulcerative colitis, urea cycle disorders, uremic pruritis, urolithiasis, uterine fibroids, vaccinia complications, varicella (chicken pox), vasoprotective, venous thromboembolism.

corresponding figures, so the numbers are correct as far as we can establish with the data at hand at the time of writing.

It must be noted that the "year" header in all tables is formally equivalent to the "year of approval" of the drug in the first country that it was approved in, though other databases may well use the "year of first introduction". We only count a drug once, even if subsequently it is approved in other countries, or for other indications in any country (see the example of trabectedin mentioned in the following section). Over the years we have noticed that there are discrepancies between sources as to the actual year, often due to differences in definitions between sources. Some reports will use the year of approval (registration by non-USA FDA equivalent organizations), while others will use the first recorded sales, and in at least one case a compound was approved but was not marketed for almost four years. We therefore have used the earliest year in such data in the absence of further information. We should also reemphasize that we have not counted "biosimilars", either when approved in the country that approved the original biologic or in any other country where a native pharmaceutical house introduced the "new agent" in that country. In the case of Taxol we have counted variations where the base molecule has been part of a new method of delivery, but this is a rare occurrence.

■ FULL DISCUSSION OF RESULTS

It should be noted that there will be repetition of some points briefly mentioned above, but in this part of the review, details and commentary will be expanded significantly. As in our previous reviews, we have, except for a few cases noted later in this review, where a therapy used NCEs plus some unapproved agent(s) in an approved combination, only covered NCEs in the present analysis. As mentioned in prior reviews, but in our opinion still worth noting, if one reads the FDA and PhRMA Web sites, the numbers of NDA approvals in any one year can be close to a hundred or so for the past few years. In the case of the FDA Drugs database, anyone using it needs to be

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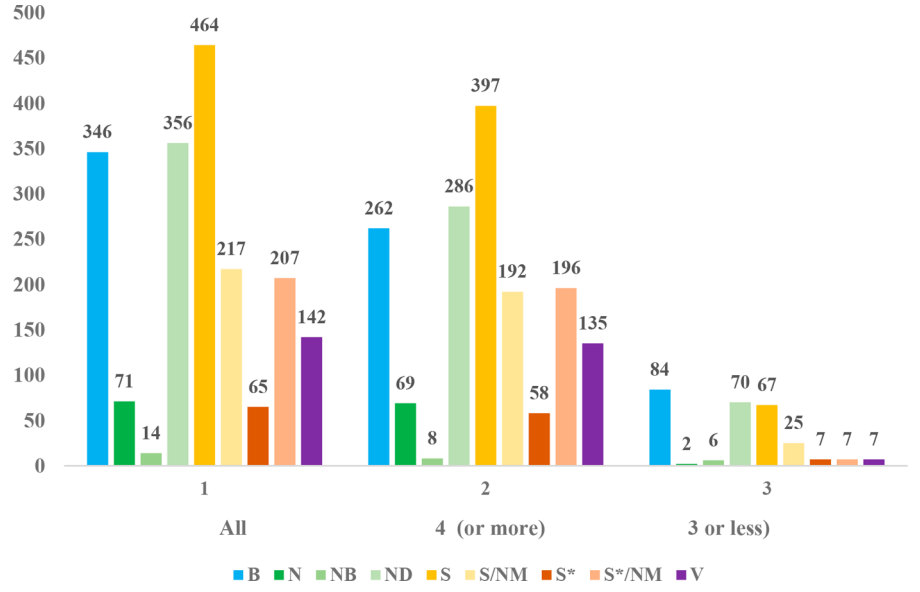

Figure 10. Disease indications/sources by number of approved drugs.

cognizant of approvals for older drugs with new and/or extended applications in such figures. Thus, there are bound to be differences due to our noting drugs the first time approved anywhere and not the first time approved by the FDA. Accordingly, there are drugs that have been approved by other countries that have been rejected by the EU or never underwent FDA supervision but have been approved elsewhere. A very good example is shown in Table 8 in the case of aplidine, rejected by the EMA and approved in Australia in 2018. Another would be trabectedin, also in Table 8, which was approved by the EMA in 2007 and finally by the FDA in 2015. We only count the latter one time in 2007. As mentioned in the Introduction, but worth reemphasizing here, using our data (see Figures 1−3), the number of true NCEs will be below what other compendia may publish.

In the almost 39 years (1981−09/2019) covered in this review and utilizing the data in the bar graph in Figure 2, a major difference was obvious in 2004, when only 24 NCEs were approved, though interestingly 7, or 29%, of that year's approvals were assigned to the ND category. There was a rebound to 52 in 2005, with 25% being N or ND but 37% being biologics (B) or vaccines (V). The next four years from 2006 to 2009 averaged 40, with 35−45% being vaccines or biologics, though in these four years, four "botanicals" (NB category) were approved. The approval roller-coaster continued, as in 2010 and 2011, the figures again dropped to 33 and 34, respectively, but then in 2012 to 2018, figures rebounded to 61, 47, 68, 69, 52, 70, and 75, respectively, with 48 in 2019 as of September 30.

We need to reiterate that our vaccine numbers are not complete, particularly in the earlier years of the period covered, so the overall numbers could increase. If we remove biologicals and vaccines, thus noting only "small molecules" (which does include peptides such as Byetta), then the figures show that over the same time frame the numbers have ranged from close to 40−45 for most of the 1989 to 2000 time frame, dropping to 18−26 from 2001 to 2012, with the exception of 2002 and 2005, when the figures climbed above 30, and in the last almost 9 years (2011 to 09/2019) the numbers now range from 27 in 2011 to 46 in 2018, and even in the first nine months of 2019, the figure is 32 for small molecules.

Now with almost 39 years of data to analyze, we have updated graphs from the 2016 review that should be of significant interest to the natural products community. In Figure 8, from 1981 to 9/2019 we have plotted a bar graph showing the percentage overall when the designations used are an "N" or a subdivision ("NB" or "ND"). The percentage of N* compounds by year is deliberately done in color so that the contribution of each type can be seen (this is also used as the graphical abstract). Over the complete $38^{3}/_{4}$ years the mean and standard deviation figures in percentages are 32 ± 9, close to the figures in the 2016 review. Then, in Figure 9, we added the "S*" source for the reasons elaborated earlier. This figure demonstrates that even in 2018, 10 of the 46 approved small-molecule drugs are "N, NB, and ND" with one S*, which account for 22% of the 46 approved NCEs that year, in 2017, the corresponding figures were 36% of the 39 approved that year, and in the 9 months of 2019, they were 28% (all ND) of the 32 small-molecule NCEs. Thus, any reader can determine their own ratios within these categories for any particular "year of interest".

Sources of All Molecules. Inspection of the rate of NCE approvals in Figures 2 and 3 shows that a significant number of NCEs are approved worldwide per year, with numbers in the last five years averaging close to 60. However, as shown in Figure 4 (radar plot), significant components of approved NCEs are biologicals with a peak in 2018, when 27 of the 75 NCEs fell into this category. Although we have not done so, one can overlay the two radar plots (Figures 3 and 4) by eye and see the influence of this category on overall numbers from 1982, when the first of these molecules were approved, with this category accounting for five of the 31 approved agents that year. The reader should also bear in mind that we deliberately have not counted "biosimilars" in this statistic, and if we had, then the number of such biologicals in the last five years would have been close to a doubling of this category. We should also comment that the overall figures from approximately 2006 now include statistics for vaccines, which ranged from a low of 1 in 2011 to 14 in 2017, and we admit that these figures are

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Table 3. Antibacterial Drugs from 01JAN1981 to 30SEP2019 Organized Alphabetically by Generic Name within Source[a]

generic name[a]	trade name	year intro.	volume	page	source
raxibacumab	ABthrax	2012	I 336061		B
anthrasil	Anthrasil	2015	I 434959		B
bezlotoxumab	Zinplava	2016	MCR 52	541	B
obiltoxaximab	Anthim	2016	MCR 52	571	B
netilimicin sulfate	Netromicine	1981	I 070366		N
micronomicin sulfate	Sagamicin	1982	I 091082		N
miokamycin	Miocamycin	1985	ARMC 21	329	N
mupirocin	Bactroban	1985	ARMC 21	330	N
carumonam	Amasulin	1988	ARMC 24	298	N
fosfomycin trometamol	Monuril	1988	I 112334		N
isepamicin	Isepacin	1988	ARMC 24	305	N
teicoplanin	Targocid	1988	ARMC 24	311	N
RV-11	Zalig	1989	ARMC 25	318	N
daptomycin	Cubicin	2003	ARMC 39	347	N
fidaxomicin	Dificid	2011	DT 48(1)	40	N
cefoperazone sodium	Cefobis	1981	I 127130		ND
cefotiam HCl	Pansporin	1981	I 091106		ND
cefsoludin sodium	Takesulin	1981	I 091108		ND
apalcillin sodium	Lumota	1982	I 091130		ND
ceftizoxime sodium	Epocelin	1982	I 070260		ND
ceftriaxone sodium	Rocephin	1982	I 091136		ND
moxalactam disodium	Shiomarin	1982	I 070301		ND
cefmenoxime HCl	Tacef	1983	ARMC 19	316	ND
ceftazidime	Fortam	1983	ARMC 19	316	ND
aztreonam	Azactam	1984	ARMC 20	315	ND
cefonicid sodium	Monocid	1984	ARMC 20	316	ND
ceforanide	Precef	1984	ARMC 20	317	ND
cefotetan disodium	Yamatetan	1984	ARMC 20	317	ND
temocillin disodium	Temopen	1984	ARMC 20	323	ND
astromycin sulfate	Fortimicin	1985	ARMC 21	324	ND
cefbuperazone sodium	Tomiporan	1985	ARMC 21	325	ND
cefpiramide sodium	Sepatren	1985	ARMC 21	325	ND
imipenem/cilastatin	Zienam	1985	ARMC 21	328	ND
rifaximin	Rifacol	1985	ARMC 21	332	ND
rokitamycin	Ricamycin	1986	ARMC 22	325	ND
aspoxicillin	Doyle	1987	ARMC 23	328	ND
cefixime	Cefspan	1987	ARMC 23	329	ND
cefminox sodium	Meicelin	1987	ARMC 23	330	ND
cefpimizole	Ajicef	1987	ARMC 23	330	ND
cefteram pivoxil	Tomiron	1987	ARMC 23	330	ND
cefuroxime axetil	Zinnat	1987	ARMC 23	331	ND
cefuzonam sodium	Cosmosin	1987	ARMC 23	331	ND
lenampicillin HCI	Varacillin	1987	ARMC 23	336	ND
rifamixin	Normix	1987	ARMC 23	341	ND
roxithromycin	Rulid	1987	ARMC 23	342	ND
sultamycillin tosylate	Unasyn	1987	ARMC 23	343	ND
azithromycin	Sunamed	1988	ARMC 24	298	ND
erythromycin acistrate	Erasis	1988	ARMC 24	301	ND
flomoxef sodium	Flumarin	1988	ARMC 24	302	ND
rifapentine	Rifampin	1988	ARMC 24	310	ND
cefpodoxime proxetil	Banan	1989	ARMC 25	310	ND
arbekacin	Habekacin	1990	ARMC 26	298	ND
cefodizime sodium	Neucef	1990	ARMC 26	300	ND
clarithromycin	Klaricid	1990	ARMC 26	302	ND
cefdinir	Cefzon	1991	ARMC 27	323	ND
cefetamet pivoxil HCl	Globocef	1992	ARMC 28	327	ND
cefpirome sulfate	Cefrom	1992	ARMC 28	328	ND
cefprozil	Cefzil	1992	ARMC 28	328	ND
ceftibuten	Seftem	1992	ARMC 28	329	ND
loracarbef	Lorabid	1992	ARMC 28	333	ND
rifabutin	Mycobutin	1992	ARMC 28	335	ND
tazobactam sodium	Tazocillin	1992	ARMC 28	336	ND
cefepime	Maxipime	1993	ARMC 29	334	ND
dirithromycin	Nortron	1993	ARMC 29	336	ND
cefditoren pivoxil	Meiact	1994	ARMC 30	297	ND
meropenem	Merrem	1994	ARMC 30	303	ND
panipenem/betamipron	Carbenin	1994	ARMC 30	305	ND
cefozopran HCl	Firstcin	1995	ARMC 31	339	ND
cefcapene pivoxil	Flomox	1997	ARMC 33	330	ND
flurithromycin ethylsuccinate	Ritro	1997	ARMC 33	333	ND
fropenam	Farom	1997	ARMC 33	334	ND
cefoselis	Wincef	1998	ARMC 34	319	ND
dalfopristin	Synercid	1999	ARMC 35	338	ND
quinupristin	Synercid	1999	ARMC 35	338	ND
telithromycin	Ketek	2001	DNP 15	35	ND
biapenem	Omegacin	2002	ARMC 38	351	ND
ertapenem sodium	Invanz	2002	ARMC 38	353	ND
doripenem	Finibax	2005	DNP 19	42	ND
tigecycline	Tygacil	2005	DNP 19	42	ND
retapamulin	Altabax	2007	ARMC 43	486	ND
ceftobiprole medocaril	Zeftera	2008	ARMC 44	589	ND
telavancin HCl	Vibativ	2009	DNP 23	15	ND
ceftaroline fosamil acetate	Teflaro	2011	DT 48(1)	40	ND
dalbavancin	Dalvance	2014	DT 51(!)	47	ND
oritavancin	Orbactiv	2014	DT 51(1)	47	ND
cetolozane/tazobactam	Zerbaxa	2014	DT 51(1)	47	ND
meropenem/vaborbactam	Vabomere	2017	DT 54	50	ND
plazomicin	Zemdri	2018	DT 55	52	ND
omadacycline	Nuzyra	2018	DT 55	51	ND
eravacycline	Xerava	2018	DT 55	51	ND
sarecycline	Seysara	2018	DT 55	50	ND
lefamulin	Xenlita	2019	I 462609		ND
imi-cilast_relebactam	Recarbrio	2019	I 891262		ND
norfloxacin	Noroxin	1983	ARMC 19	322	S
ofloxacin	Tarivid	1985	ARMC 21	331	S
pefloxacin mesylate	Perflacine	1985	ARMC 21	331	S
ciprofloxacin	Ciprobay	1986	ARMC 22	318	S
enoxacin	Flumark	1986	ARMC 22	320	S
taurolidine	Taurolin	1988	I 107771		S
lomefloxacin	Uniquin	1989	ARMC 25	315	S
tosufloxacin	Ozex	1990	ARMC 26	310	S
temafloxacin hydrochloride	Temac	1991	ARMC 27	334	S
fleroxacin	Quinodis	1992	ARMC 28	331	S
rufloxacin hydrochloride	Qari	1992	ARMC 28	335	S
levofloxacin	Floxacin	1993	ARMC 29	340	S
nadifloxacin	Acuatim	1993	ARMC 29	340	S
sparfloxacin	Spara	1993	ARMC 29	345	S

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Table 3. continued

generic name[a]	trade name	year intro.	volume	page	source
grepafloxacin	Vaxor	1997	DNP 11	23	S
trovafloxacin mesylate	Trovan	1998	ARMC 34	332	S
gatilfloxacin	Tequin	1999	ARMC 35	340	S
moxifloxacin HCl	Avelox	1999	ARMC 35	343	S
linezolid	Zyvox	2000	DNP 14	21	S
balafloxacin	Q-Roxin	2002	ARMC 38	351	S
pazufloxacin	Pasil	2002	ARMC 38	364	S
prulifloxacin	Sword	2002	ARMC 38	366	S
gemifloxacin mesilate	Factive	2003	ARMC 40	458	S
garenoxacin	Geninax	2007	ARMC 43	471	S
besifloxacin	Besivance	2009	DNP 23	20	S
bedaquiline	Sirturo	2012	I 386239		S
tedizolid phosphate sodium	Sivextro	2014	DT 51(1)	47	S
nemonoxacin	Taigexyn	2014	DT 51(1)	48	S
finafloxacin hydrochloride	Xtoro	2014	DT 51(1)	48	S
astrodimer	Vivagel	2015	DT 52	55	S
nemonoxacin	Taigexyn	2015	I 401112		S
ozenoxacin	Zebiax	2015	MCR 51	503	S
zabofloxacin hydrochloride	Zabolante	2015	MCR 51	526	S
delafloxacin meglumine	Baxdela	2017	MCR 53	614	S
lasculfloxacin	Lasvic	2019	I 818081		S
pretomanid		2019	I 241160		S
brodimoprin	Hyprim	1993	ARMC 29	333	S*/NM
ACWY meningoccal PS vacc.	Mencevax	1981	I 420128		V
h influenzae b vaccine	Hibtitek	1989	DNP 03	24	V
h influenzae b vaccine	Prohibit	1989	DNP 03	24	V
oral cholera vaccine	Orochol	1994	DNP 08	30	V
vi polysacch. typhoid vacc	Typherix	1998	DNP 12	35	V
meningococcal vaccine	Menigetec	1999	DNP 14	22	V
meningococcal vaccine	NeisVac-C	2000	DNP 14	22	V
meningococcal vaccine	Menjugate	2000	DNP 14	22	V
pneumococcal vaccine	Prevnar	2000	DNP 14	22	V
hexavalent vaccine	Hexavac	2000	DNP 14	22	V
hexavalent vaccine	Infantrix HeXa	2000	DNP 14	22	V
dpt vaccines	Daptacel	2002	I 319668		V
meningitis b vaccine	MeNZB	2004	DNP 18	29	V
MCV-4	Menactra	2005	DNP 19	43	V
DTPw-HepB-Hib	Quinvaxem	2006	DNP 20	26	V
DTaP vaccine	Tribik	2006	I 847926		V
	Prevenar 13	2009	DNP 23	17	V
	Synflorix	2009	DNP 23	17	V
menACWY-CRM	Menveo	2010	I 341212		V
PsA-TT	MenAfriVac	2010	I 437718		V
hib-mency-tt	Menhibrix	2012	I 421742		V
BK-4SP	Tetrabik	2012	I 697562		V
	Quattrovac	2012	I 770186		V
MenACWY-TT	Nimenrix	2012	I 421745		V
	Typbar	2013	DT 50(1)	68	V
	Bexsero	2013	DT 50(1)	69	V
botulism antitoxin	Bat	2013	DT 50(1)	77	V
MnB rLP2086	Trumenba	2014	DT 51(1)	51	V
DPT-IPV	Squarekids	2014	I 804432		V
CVD 103-HgR	Vaxchora	2016	I 220669		V
DTP-HepB-Polio-Hib	Vaxelis	2016	DT 53	45	V
GC-1107	G.C.TD Vaccine	2018	DT 55	59	V

[a]Where there is no generic or trade name, the table has a blank entry in the corresponding column.

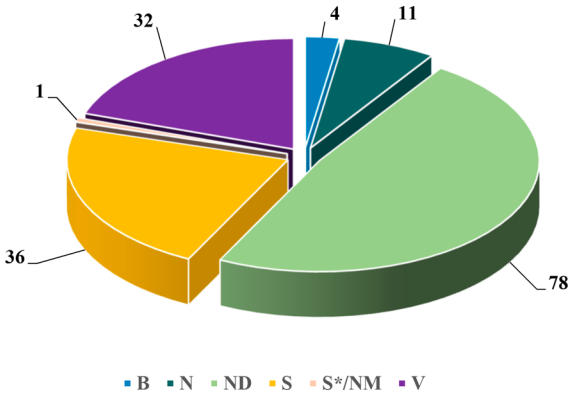

Figure 11. Antibacterial drugs by source.

probably on the low side, as tracking down molecules approved in the Asian mainland and the CIS is difficult.

As was shown in the 2016 review, the numbers of all NCEs that fall into the categories of biological ("B") or vaccines ("V") are still highly significant, with their figures totaling 488 of the 1881 NCEs (25.9%) compared to the 356 of 1562 NCEs (22.8%) in the 2016 review. Inspection of Figures 2 and 3 shows the significant proportion that these two categories hold in the number of approved drugs from 2000, where, in some years, these categories accounted for ca. 50% of all approvals.

Sources of Small Molecules. Inspection of Figure 5 shows the sources of the 1394 small molecules (i.e., minus the "B" and "V" categories) as a pie chart, Figure 6 is the corresponding bar chart, and Figure 7 shows the corresponding radar plot. These three figures demonstrate that even at the end of the third quarter of 2019 the "direct or direct from" natural products field (N*) is still producing, with 441 of the 1394 small molecules (32%) falling into this overall category over the complete time period. The percentage of "N*" NCEs is shown by year in the Figure 8 bar graph. The mean and standard deviation for the almost 39 years covered is 32 ± 9%, without including any of the natural product-inspired classifications (S*, S*/NM, and S/NM). In the 2016 review we only used data from 2000, but for the present analysis we went back to 1981. In 1991 and 1997, the percentage was 20 or lower, which reduced the overall average, and then the sources accounted for ~40% of all "small molecules" in the

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Table 4. Antifungal Drugs from 01JAN1981 to 30SEP2019, Organized Alphabetically by Generic Name within Source

generic name	trade name	year intro	volume	page	source
interferon gamma-n1	OGamma100	1996	DNP 10	13	B
caspofungin acetate	Cancidas	2001	DNP 15	36	ND
micafungin sodium	Fungard	2002	ARMC 38	360	ND
anidulafungin	Eraxis	2006	DNP 20	24	ND
ketoconazole	Nizoral	1981	I 116505		S
ciclopirox olamine	Loprox	1982	I 070449		S
oxiconazole nitrate	Oceral	1983	ARMC 19	322	S
terconazole	Gyno-Terazol	1983	ARMC 19	324	S
tioconazole	Trosyl	1983	ARMC 19	324	S
naftifine HCI	Exoderil	1984	ARMC 20	321	S
sulconazole nitrate	Exelderm	1985	ARMC 21	332	S
butoconazole	Femstat	1986	ARMC 22	318	S
cloconazole HCI	Pilzcin	1986	ARMC 22	318	S
fenticonazole nitrate	Lomexin	1987	ARMC 23	334	S
fluconazole	Diflucan	1988	ARMC 24	303	S
itraconazole	Sporanox	1988	ARMC 24	305	S
amorolfine HCl	Loceryl	1991	ARMC 27	322	S
sertaconazole nitrate	Dermofix	1992	ARMC 28	336	S
neticonazole HCI	Atolant	1993	ARMC 29	341	S
lanoconazole	Astat	1994	ARMC 30	302	S
flutrimazole	Micetal	1995	ARMC 31	343	S
voriconazole	Vfend	2002	ARMC 38	370	S
fosfluconazole	Prodif	2003	DNP 17	49	S
eberconazole	Ebernet	2005	DNP 19	42	S
luliconazole	Lulicon	2005	DNP 19	42	S
posaconazole	Noxafil	2005	DNP 19	42	S
sitafloxacin hydrate	Gracevit	2008	DNP 22	15	S
efinaconazole	Jublia	2013	DT 50(1)	66	S
tavaborole	Kerydin	2014	DT 51(1)	51	S
isavuconazonium sulfate	Cresemba	2015	MCR 51	485	S
fosravuconazole	Nailin	2018	DT 55	56	S
terbinafine HCl	Lamisil	1991	ARMC 27	334	S/NM
butenafine HCl	Mentax	1992	ARMC 28	327	S/NM
liranaftate	Zefnart	2000	DNP 14	21	S/NM

Figure 12. Antifungal drugs by source.

years 2000−2008, dropped to ∼20% in 2009, followed by a rebound to 45% in 2010, and then fluctuated from a low of ∼13% in 2013 and 2015 to between 25% and 33% in the other years of the second decade of the 21st century.

In addition to this plot, we have also provided the data shown in the Figure 9 bar graph, where we have now added the "S*" classification to the "N*" figures. As described earlier, we justify this addition as the "S*" classification to cover compounds that utilize an NP pharmacophore even though they are synthetic. By using the actual figures shown in this bar graph, the individual year's figures and corresponding sources may be determined and used as the reader desires. The total number of these small molecules amounted to 506, with the addition of the 65 "S*" compounds, bringing the overall percentage for the almost 39 years to 36.3% of the 1394 small molecules identified in that time frame. These figures emphasize the continued influence of "other than totally synthetic compounds" (meaning de novo discovery not based on any NP pharmacophore) in the discovery of small-molecule drugs. However, we would be remiss if we did not point out that there are a number of disease states for which only synthetic compounds have been of utility as drugs. These will be commented on below as the disease tables are presented.

Analyses of Diseases Treated by the NCEs over the $38^{3}/_{4}$ Years. In Table 2 we have continued our custom of splitting the disease areas into those where four or more drugs have been approved since the beginning of 1981, so that the individual contribution of the various sources can be seen. Then, we have simply listed the other disease areas where three

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Table 5. Antiviral Drugs from 01JAN1981 to 30SEP2019, Organized Alphabetically by Generic Name within Source[a,b]

generic name	trade name	year intro.	volume	page	source
interferon alfa-2b	Viraferon	1985	I 165805		B
interferon beta	Frone	1985	I 115091		B
interferon alfa-n1	Wellferon	1986	I 125561		B
interferon alfa	Alfaferone	1987	I 215443		B
interferon alfa-n3	Alferon N	1990	DNP 04	104	B
resp syncytial virus IG	RespiGam	1996	DNP 10	11	B
thymalfasin	Zadaxin	1996	DNP 10	11	B
interferon alfacon-1	Infergen	1997	ARMC 33	336	B
palivizumab	Synagis	1998	DNP 12	33	B
peginterferon alfa-2b	Pegintron	2000	DNP 14	18	B
peginterferon alfa-2a	Pegasys	2001	DNP 15	34	B
immunoglobulin (IV)	Gammagard Liquid	2005	I 231564		B
	Oralgen	2007	I 415378		B
IGIV-HB	Niuliva	2009	DNP 23	16	B
pegylated interferon alfa-2b	Paigebin	2016	DT 53	42	B
ibalizumab	Trogarzo	2018	DT 55	56	B
rIFN-2ab	Novaferon	2018	I 649439		B
oseltamivir	Tamiflu	1999	ARMC 35	346	ND
zanamivir	Relenza	1999	ARMC 35	352	ND
tenofovir disoproxil fumarate	Viread	2001	DNP 15	37	ND
enfuvirtide	Fuzeon	2003	ARMC 39	350	ND
laninamivir octanoate	Inavir	2010	I 340894		ND
tenofovir disoproxil orotate	virreal	2017	I 874960		ND
rimantadine HCI	Roflual	1987	ARMC 23	342	S
foscarnet sodium	Foscavir	1989	ARMC 25	313	S
propagermanium	Serosion	1994	ARMC 30	308	S
nevirapine	Viramune	1996	ARMC 32	313	S
delavirdine mesylate	Rescriptor	1997	ARMC 33	331	S
imiquimod	Aldara	1997	ARMC 33	335	S
efavirenz	Sustiva	1998	ARMC 34	321	S
maraviroc	Celsentri	2007	ARMC 43	478	S
raltegravir potassium	Isentress	2007	ARMC 43	484	S
rilpivirine hydrochloride	Edurant	2011	DT 48(1)	41	S
dolutegravir	Tivicay	2013	DT 50(1)	63	S
elvitegravir	Viteka	2013	DT 50(1)	63	S
daclatasvir dihydrochloride	Daklinza	2014	DT 51(1)	48	S
dasabuvir	Exviera	2014	DT 51(1)	50	S
sofosbuvir/ velpatasvir	Epclusa	2016	MCR 52	587	S
amenamevir	amenalief	2017	DT 54	50	S
elpivrine	Elipida	2017	MCR 53	622	S
letermovir	Prevymis	2017	MCR 53	641	S
doravirine	Pifeltro	2018	DT 55	55	S
acyclovir	Zovirax	1981	I 091119		S*
inosine pranobex	Imunovir	1981	I 277341		S*
zidovudine	Retrovir	1987	ARMC 23	345	S*
epervudine	Hevizos	1988	I 157373		S*
ganciclovir	Cymevene	1988	ARMC 24	303	S*
didanosine	Videx	1991	ARMC 27	326	S*
zalcitabine	Hivid	1992	ARMC 28	338	S*
sorivudine	Usevir	1993	ARMC 29	345	S*
famciclovir	Famvir	1994	ARMC 30	300	S*
stavudine	Zerit	1994	ARMC 30	311	S*
lamivudine	Epivir	1995	ARMC 31	345	S*
valaciclovir HCl	Valtrex	1995	ARMC 31	352	S*
cidofovir	Vistide	1996	ARMC 32	306	S*
penciclovir	Vectavir	1996	ARMC 32	314	S*
abacavir sulfate	Ziagen	1999	ARMC 35	333	S*
valganciclovir	Valcyte	2001	DNP 15	36	S*
adefovir dipivoxil	Hepsera	2002	ARMC 38	348	S*
emtricitabine	Emtriva	2003	ARMC 39	350	S*
entecavir	Baraclude	2005	DNP 19	39	S*
telbivudine	Sebivo	2006	DNP 20	22	S*
clevudine	Levovir	2007	ARMC 43	466	S*
etravirine	Intelence	2008	DNP 22	15	S*
sofosbuvir	Sovaldi	2013	DT 50(1)	64	S*
beclabuvir/ asunaprevir/ daclatavir		2016	MCR 52	539	S*
tenofovir alafenamide fumarate	Vemlidy	2016	DT 53	41	S*
sofosbuvir/ voxilaprevir/ velpatavir	Vosevi	2017	MCR 53	675	S*
saquinavir mesylate	Invirase	1995	ARMC 31	349	S*/ NM
indinavir sulfate	Crixivan	1996	ARMC 32	310	S*/ NM
ritonavir	Norvir	1996	ARMC 32	317	S*/ NM
neflinavir mesylate	Viracept	1997	ARMC 33	340	S*/ NM
fomivirsen sodium	Vitravene	1998	ARMC 34	323	S*/ NM
amprenavir	Agenerase	1999	ARMC 35	334	S*/ NM
lopinavir	Kaletra	2000	ARMC 36	310	S*/ NM
atazanavir	Reyataz	2003	ARMC 39	342	S*/ NM
fosamprenevir	Lexiva	2003	ARMC 39	353	S*/ NM
tipranavir	Aptivus	2005	DNP 19	42	S*/ NM
favipiravir	Avigan	2006	DT 51(1	50	S*/ NM
boceprevir	Victrelis	2011	DT 48(1)	41	S*/ NM
telaprevir	Incivek	2011	DT 48(1)	41	S*/ NM
simeprevir	Sovriad	2013	DT 50(1)	63	S*/ NM
vaniprevir	Vanihep	2014	DT 51(1)	49	S*/ NM
ombitasvir	Viekira Pak	2014	DT 51(1)	50	S*/ NM
paritaprevir	Viekira Pak	2014	DT 51(1)	50	S*/ NM
narlaprevir	Arlansa	2016	I 445764		S*/ NM
glecaprevir/ pibrentasvir	Maviret	2017	MCR 53	631	S*/ NM
danoprevir	Ganovo	2018	DT 55	55	S*/ NM
albuvirtide	Aikening	2018	DT 55	55	S*/ NM

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Table 5. continued

generic name	trade name	year intro.	volume	page	source
darunavir	Prezista	2006	DNP 20	25	S/NM
peramivir	PeramiFlu	2010	I 273549		S/NM
cobicistat	Tybost	2013	DT 50(1)	63	S/NM
asunaprevir	Sunvepra	2014	DT 51(1)	48	S/NM
ledipasvir	Harvoni	2014	DT 51(1)	48	S/NM
grazoprevir	Grazyna	2016	MCR 52	549	S/NM
elbasvir	Erelsa	2016	MCR 52	549	S/NM
baloxavir marboxil	Xofluza	2018	DT 55	52	S/NM
tecovirimat	Arestvyr	2018	DT 55	54	S/NM
rubella vaccine	Ervevax	1985	I 115078		V
hepatitis b vaccine	Engerix B	1987	I 137797		V
hepatitis a vaccine	Havrix	1992	DNP 06	99	V
Atten. chicken pox vac	Merieux Var vac	1993	DNP 07	31	V
hepatitis b vaccine	Biken-HB	1993	DNP 07	31	V
hepatitis a vaccine	Aimmugen	1995	DNP 09	23	V
varicella virus vaccine	Varivax	1995	DNP 09	25	V
hepatitis a vaccine	Vaqta	1996	DNP 10	11	V
inact hepatitis a vaccine	Avaxim	1996	DNP 10	12	V
hepatitis b vaccine	Meinyu	1997	DNP 11	24	V
rotavirus vaccine	Rota-Shield	1998	DNP 12	35	V
hepatitis b vaccine	Bio-Hep B	2000	DNP 14	22	V
hepatitis b vaccine	Hepacure	2000	DNP 14	22	V
hepatitis A and B vac	Ambirix	2003	I 334416		V
influenza virus (live)	FluMist	2003	ARMC 39	353	V
influenza vaccine	Invivac	2004	I 391186		V
	Bilive	2005	DNP 19	43	V
MR vaccine	Mearubik	2005	DNP 19	44	V
hepatitis B vaccine	Fendrix	2005	DNP 19	43	V
rotavirus vaccine	Rotarix	2005	DNP 18	29	V
	VariZIG	2005	I 230590		V
anti-Hep B immunoglobulin	HepaGam B	2006	DNP 20	27	V
hpv vaccine	Gardasil	2006	DNP 20	26	V
rotavirus vaccine	Rotateq	2006	DNP 20	26	V
zoster vaccine live	Zostavax	2006	DNP 20	26	V
antirabies vaccine	Rabirix	2006	DNP 20	27	V
rec hepatitis B vaccine	Supervax	2006	DNP 20	27	V
split influenza vaccine	Anflu	2006	DNP 20	26	V
	Optaflu	2007	I 410266		V
	Daronix	2007	I 427024		V
H5N1 avian flu vaccine		2007	I 440743		V
influenza virus vaccine	Afluria	2007	I 449226		V
	ACAM-2000	2007	I 328985		V
influenza vaccine	Optaflu	2008	DNP 22	16	V
GSK-1562902A	Prepandrix	2008	DNP 22	16	V
CSL-401	Panvax	2008	DNP 22	16	V
	Panflu	2008	DNP 22	16	V
	Grippol Neo	2009	DNP 23	16	V
	Focetria	2009	DNP 23	17	V
	Pandremix	2009	DNP 23	17	V
	Celtura	2009	DNP 23	17	V
	Panenza	2009	DNP 23	17	V
	Fluval P	2009	DNP 23	17	V
	Celvapan	2009	DNP 23	17	V
	Vaxiflu-S	2010	I 698015		V
VCIV	PreFluCel	2010	I 444826		V
Influenza A (H1N1) monovalent		2010	I 678265		V
HN-VAC	HNVAC	2010	I 684608		V
measles/rubella vaccine		2011	DT 48(1)	44	V
HEV-239	Hecolin	2012	I 656910		V
Medi-3250	FluMist Quadrivalent	2012	I 669909		V
	Vepacel	2012	I 768351		V
chimerivax-JE	Imojev	2012	I 292954		V
GSK-2282512A	Fluarix Quad.	2012	I 709665		V
FLU-Q-QIV	Flulaval Quadrivalent	2013	DT 50(1)	68	V
	Fluzone Quad.	2013	DT 50(1)	68	V
BBIL/JEV	Jenvac	2013	DT 50(1)	68	V
	Imvanex	2013	DT 50(1)	69	V
KD-295		2014	DT 51(1)	52	V
9vHPV	Gardasil 9	2014	DT 51(1)	52	V
H5N1 Avian Flu Vac	VN-101	2014	I 796803		V
ChimeriVax-Dengue	Dengvaxia	2015	DT 52	59	V
GC-3110A	GCFLU Quad.	2015	DT 52	58	V
NBP-607	SKYCellflu	2015	DT 52	58	V
NBP-607-QIV	SKYCellflu Quadrivalent	2015	DT 52	58	V
ORV-116E	Rotavac	2015	DT 52	58	V
	Ai Bi Wei	2015	DT 52	58	V
Gam Evac Combi		2015	I 972727		V
RIV-4	Flublok-Q	2016	DT 53	44	V
	Afluria Quad.	2016	DT 53	44	V
	Cadiflu-S	2016	DT 53	44	V
	Inlive	2016	DT 53	44	V
	P/LAIV	2016	DT 53	45	V
	Vaxigriptetra	2016	DT 54	55	V
	Flucelvax Quad.	2016	DT 53	44	V
	VaxiFlu-4	2017	DT 54	56	V
Ad5-EBOV		2017	DT 54	56	V
DTwP-HepB-Hib-IPV	Easysix	2017	DT 54	55	V
GSK-1437173A	Shingrix	2017	DT 54	55	V
HBV-ISS	Heplisav-B	2017	DT 54	55	V
NBP-608	SKYZoster	2017	DT 54	56	V
	Vaxigrip QIV	2017	I 763740		V
	AdimFlu-S (QIS)	2017	DT 54	56	V
YS-ON-001	Yivyka	2017	I 880215		V
	Grippol Quad.	2018	DT 55	59	V
	Picovax	2019	I 868690		V
	Hexyon	2013	DT 50(1)	69	V

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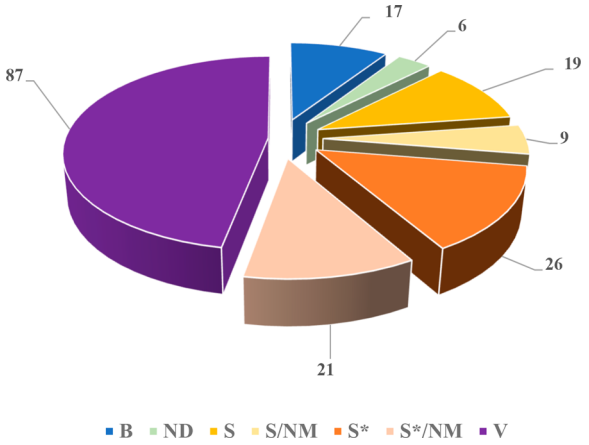

Figure 13. Antiviral Drugs by Source.

Table 6. Antiparasitic Drugs from 10JAN1981 to 30SEP2019, Organized Alphabetically by Generic Name within Source

generic name	trade name	year intro.	volume	page	source
artemisinin	Artemisin	1987	ARMC 23	327	N
ivermectin	Mectizan	1987	ARMC 23	336	N
mefloquine HCl	Fansimef	1985	ARMC 21	329	ND
artemether	Artemetheri	1987	I 90712		ND
artenusate	Arinate	1987	I 91299		ND
eflornithine HCl	Ornidyl	1990	DNP 04	104	ND
arteether	Artemotil	2000	DNP 14	22	ND
moxidectin		2018	DT 55	57	ND
tafenoquine succinate	Etaquine	2018	DT 55	56	ND
albendazole	Eskazole	1982	I 129625		S
quinfamide	Amenox	1984	ARMC 20	322	S
lumefantrine		1987	I 269095		S
halofantrine	Halfan	1988	ARMC 24	304	S
delamanid	Deltyba	2014	DF 51(1)	48	S
fexinidazole	Fexinidazole Winthrop	2019	I 308225		S
atovaquone	Mepron	1992	ARMC 28	326	S*
bulaquine/ chloroquine	Aablaquin	2000	DNP 14	22	S*
arterolane/ piperaquine	Synriam	2012	I 466970		S*
trichomonas vaccine	Gynatren	1986	I 125543		V
GSK-257049	Mosquirix	2015	I 433552		V

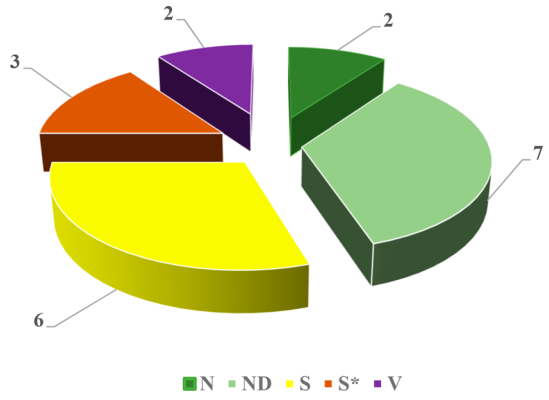

Figure 14. Antiparasitic drugs by source.

or fewer drugs were approved together with a simple summation of sources. As mentioned earlier, we have kept to this format rather than placing the fewer than four drug/disease categories in the Supporting Information, as readers can then easily determine where a given disease moiety falls in terms of number of approved drugs in the time frame used. Next, in Figure 10 we have used a simple bar graph to further demonstrate the influence of the various sources. In this plot, the first "series" covers all diseases, for the 1881 NCEs, the second "series", the four or more diseases covered by 1602 NCEs, and the third "series", the three or fewer disease indications covered by the remaining 279 NCEs. It should also be noted that in contrast to our 2012 review,[4] but as we mentioned in the 2016 review,[5] we have continued to combine drugs against diabetes into one category not two.

A further analysis of Table 2 demonstrates that in this time period the major disease areas that have had four or more drugs approved by the relevant authorities, with the drug sources being mainly the pharmaceutical industry, and in rare cases governmental and/or academic groups, continue to be the following: infectious diseases, including microbial, parasitic, and viral, with 402 (25%); cancer with 247 (15.4%); hypertension with 82 (5.1%); antidiabetic with 63 (3.9%); inflammation with 53 (3.3%). For each, there have been more than 50 approved drug therapies.

Disease Areas without Natural Product Drugs. As reported in our earlier analyses,[1−5] there are still significant therapeutic classes where the available drugs are totally synthetic at the present time. These include antihistamines, diuretics, and hypnotics for indications with four or more approved drugs (cf. Table 2), and, as found in the earlier reviews, there are still a substantial number of indications in which there are three or fewer approved drugs that are also totally synthetic. The underlying reasons for the "all-synthetic drug" disease areas are well beyond the scope of this review, but almost certainly involve access to the disease site (crossing the blood brain barrier for example), first pass metabolism by body processes, and other pharmacological processes. Readers who are interested can access the structures using other chemical databases, as the diseases are identified in Table 2, with a total listing of all drugs in the Supporting Information. By contrast, as mentioned in our earlier reviews from 2003,[2−5] due to the introduction of the "NM" subcategory in the 2003 review, indications such as antidepressants, bronchodilators, and cardiotonics continue to have substantial numbers that, although formally "S" or "S*", fall into the "S/NM" or "S*/NM subcategories, as the information in the literature points to their interactions at active sites as competitive inhibitors and/or agonists/antagonists depending upon their pharmacology. As mentioned earlier, we have combined some disease classes, particularly in antidiabetics and hemophilia; thus a direct comparison of Table 2 in this review with its predecessor tables needs to take such modifications into account.

Economic Value of Drugs. The numbers of approved drugs/disease do not correlate with the "value" as measured by sales, though one has to be careful in assessing and/or using such figures, as the term "sales" can and does have a variety of definitions. The major "information source" in the USA is the prescription sales data collected by IMS, but this definition can vary, and sales data from overseas can also be a problem to obtain, characterize, and audit.

From a report in 2018 by Andrew Liu published by Fierce Pharma (https://www.fiercepharma.com/from-old-behemoth-

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Table 7. All Anti-infective Agents, Sorted by Source, 01JAN1981−30SEP2019

drug class	B	N	ND	S	S/NM	S*	S*/NM	V	total
antibacterial	4	11	78	36			1	32	162
antifungal	1		3	27	3				34
antiviral	17		6	19	9	26	21	87	185
antiparasitic		2	7	6		3		2	20
total	22	13	94	88	12	29	22	121	401
percent all (n = 401)	5.5	3.2	23.4	22.1	3	7.2	5.5	30.1	
percent small (n = 258)		5	36.3	34.4	4.6	11.2	8.5		

lipitor-to-new-king-humira-u-s-bestselling-drugs-over-25-years), which covers up through 2017, the best-selling drug of the last 25 years is still atorvastatin (Lipitor), a hypocholesterolemic descended directly from a microbial natural product, with total sales in the USA from 1992 to 2017 of $94.67 billion. The next is the biologic Humira, with sales of $75.78 billion, the third is the totally synthetic antiulcer treatment Nexium, with sales of $72.5 billion, and the fourth is the Advair inhaler combination of a modified corticosteroid and the beta-2-adrenergic agent (a combination of two ND compounds), with sales of $69.1 billion. So natural product-derived molecules are numbers 1 and 4 in the USA sales chart up through the end of 2017. With the advent of new biologics in anticancer and anti-inflammatory treatment protocols, these cumulative figures could well be exceeded in the next few years.

Anti-infective Agents. Rather than discussing these agents as a combined category, we will discuss them individually depending upon which particular infection class they are directed against, though in the case of some NP-based compounds derived from artemisinin they have activities that may well lead to antiviral compounds and/or anticancer agents in future years. These will be mentioned during the discussion on antiparasitics.

Antibacterial Agents. Inspection of Figure 11 shows that 36 of the 162 agents approved in the time frame of this review were biologics (4) or vaccines (32), predominantly as prophylactic agents for young children. None of these will be further discussed in this section. Of the remaining 126 agents, 78, or just over 48% of the total, fell into the N or ND categories, with 36 (22.2%) being totally synthetic (mainly quinolone-based), though interestingly the base molecule for these, nalidixic acid, was an unexpected antibacterial byproduct of syntheses around attempts to synthesize quinine-based entities. There is one outlier from 1993, brodimoprin, which is the sole S*/NM agent in all of the years covered.

What is of significant interest was the approval in the time from 2017 to 2019 of one derivative of the aminoglycoside sisomicin (**6**), which was never approved in the USA, to yield plazomicin (**7**), which was approved by the FDA in 2018. It should be noted, with dismay, that the company that developed this drug filed for bankruptcy in 2019, less than a year after approval, as the sales figures amounted to ∼$80 million, around a tenth of the cost to develop the drug. Following on from modifications of aminoglycosides, in late 2018, three tetracycline-based agents were also approved, omadacycline (**8**), eravacycline (**9**), and sarecycline (**10**), followed by one more ND compound, lefamulin (**11**), which is a derivative of the original fungal natural product pleuromutilin, first reported in 1950. There are also two "interesting combinations" where the FDA has approved defined mixtures of agents that are composed of earlier approved agent(s) with another that is not yet approved. These are Recarbrio, a mixture of imipenem/cilastin (approved in 1985) with the β-lactamase inhibitor relebactam (**12**), which though in phase III trials, is not an approved drug in its own right. The other, a defined mixture of meropenem (approved in 1994) and the β-lactamase inhibitor vaborbactam (**13**), was approved in 2017 by the FDA though vaborbactam was in phase I trials. These latter two "mixtures" are similar to the FDA approvals referred to in the 2016 review when discussing the "cocktails" used in the treatment of hepatitis C infections.

The colistin-degrading plasmid originally reported in 2015 by Liu et al.[119] and initially discussed in the 2016 review has now moved to some of the ESKAPE pathogens; thus the agents that were still active against such pathogens, the peptidic colistins, are now degradable by this plasmid.[120−122] Accordingly, new active antibiotics are definitively required, but there are now very few large pharmaceutical companies worldwide that are willing to spend the funds necessary under the current approval systems. The bankruptcy of the small company (Achoagen) that developed plazomicin (see above) is an example of just the postapproval financial problems, let alone the regulatory and financial hurdles under current approval systems.

Although not listed in the tables, nor used in the analyses as it occurred after the end of September 2019 deadline, the FDA in the middle of November 2019 approved the very interesting combined cephalosporin−siderophore cefiderocol (**14**) developed by the Japanese company Shionogi. So, even close to 75 years since the discovery of tetracyclines, aminoglycosides, and cephalosporins, and 60 in the case of the "mutulins", these basic natural product chemical skeletons are still valid leads to novel agents.

Antifungal Agents. Though new fungal diseases are being reported, frequently from patients whose immune systems are compromised for one reason or another, in this disease area, as can be seen from Table 4 and the pie chart, Figure 12, only two agents, both of which are synthetic, have been approved since our last review, isavuconazonium sulfate (**15**) and fosravuconazole (**16**). There are two natural product-based compounds in phase III trials, which may well help improve the natural product statistics in the relatively near future. These are enfumafungin (**17**), a triterpene that led to the semisynthetic ibrexafungerp (**18**), which is in four current phase III trials, together with one based on the echinocandin skeleton, rezafungin (**19**), which is in one phase III trial and one phase I safety trial. It should be emphasized that phase III trials in anti-infectives are randomized comparator studies in diseased patients against the current best treatment.

Antiviral Agents. In the antiviral area as mentioned earlier, a very significant number of approved agents are vaccines, often directed against various serotypes of influenza, as would be expected from the many flu outbreaks. From 2015 to 09/

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Table 8. Anticancer Drugs from 01JAN81 to 30SEP2019, Organized Alphabetically by Generic Name within Source[a]

generic name	trade name	year intro.	volume	page	source
	Rexin-G	2007	I 346431		B
131I-chTNT		2007	I 393351		B
alemtuzumab	Campath	2001	DNP 15	38	B
atezolizumab	Tecentriq	2016	MCR 52	537	B
avelumab	Bavencio	2017	MCR 53	599	B
axicabtagene ciloleucel	Yescarta	2017	DT 54	62	B
bevacizumab	Avastin	2004	ARMC 40	450	B
blinatumomab	Blincyto	2014	DT 51(1)	55	B
calaspargase pegol	Oncaspar-IV	2018	DT 55	63	B
catumaxomab	Removab	2009	DNP 23	18	B
celmoleukin	Celeuk	1992	DNP 06	102	B
cemipilimab	Libtayo	2018	I 76513		B
cetuximab	Erbitux	2003	ARMC 39	346	B
daratumumab	Darzalex	2015	MCR 51	471	B
denileukin diftitox	Ontak	1999	ARMC 35	338	B
dinutuximab	Unituxin	2015	MCR 51	473	B
dinutuximab beta	Isqette	2017	DT 54	58	B
durvalumab	Imfinzi	2017	MCR 53	620	B
elotuzumab	Empliciti	2015	MCR 51	475	B
H-101		2005	DNP 19	46	B
HR-301210	Camrelizumab	2019	I 891978		B
ibritumomab	Zevalin	2002	ARMC 38	359	B
interferon alfa2a	Roferon-A	1986	I 204503		B
interferon, gamma-1a	Biogamma	1992	ARMC 28	332	B
interleukin-2	Proleukin	1989	ARMC 25	314	B
ipilimumab	Yervoy	2011	DT 48(1)	45	B
mobenakin	Octin	1999	ARMC 35	345	B
mogamulizumab	Poteligeo	2012	I 433141		B
moxetumomab	Lumoxiti	2018	DT 55	63	B
nalotimagene carmaleucel	Zalmoxis	2016	DT 53	48	B
necitumumab	Portrazza	2015	MCR 51	498	B
nimotuzumab	BIOMAb EFGR	2006	DNP 20	29	B
nivolumab	Optivo	2014	DT 51(1)	55	B
obinutuzumab	Gazyva	2013	DT 50(1)	70	B
ofatumumab	Arzerra	2009	DNP 23	18	B
olaratumab	Lartruvo	2016	MCR 52	572	B
panitumumab	Vectibix	2006	DNP 20	28	B
pegaspargase	Oncaspar	1994	ARMC 30	306	B
pembrolizumab	Keytruda	2014	DT 51(1)	55	B
pertuzumab	Omnitarg	2012	I 300439		B
racotumomab	Vaxira	2013	DT 50(1)	72	B
ramucirumab	Cyramza	2014	DT 51(1)	55	B
rituximab	Rituxan	1997	DNP 11	25	B
sintilimab	Tyvyt	2018	DT 55	61	B
sipuleucel-T	Provenge	2010	I 259673		B
tagraxofusp	Elzonris	2018	DT 55	64	B
tasonermin	Beromun	1999	ARMC 35	349	B
teceleukin	Imumace	1992	DNP 06	102	B
tisagenlecleucel	Kymriah	2017	DT 54	62	B
toripalimab	TeRuiPuLi	2018	DT 55	61	B
tositumomab	Bexxar	2003	ARMC 39	364	B
trastuzumab	Herceptin	1998	DNP 12	35	B
	PICN	2014	DT 51(1)	58	N
aclarubicin	Aclacin	1981	I 090013		N
aminolevulinic acid	Levulan	2000	DNP 14	20	N
angiotensin II	Delivert	1994	ARMC 30	296	N
aplidine	Aplidin	2018	DT 55	64	N
arglabin	?	1999	ARMC 35	335	N
homoharringtonine	Ceflatonin	2012	I 090682		N
ingenol mebutate	Picato	2012	I 328987		N
masoprocol	Actinex	1992	ARMC 28	333	N

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Table 8. continued

generic name	trade name	year intro.	volume	page	source
paclitaxel	Taxol	1993	ARMC 29	342	N
paclitaxel liposomal	Lipusu	2003	I 834256		N
paclitaxel nanoparticles	Abraxane	2005	DNP 19	45	N
paclitaxel nanoparticles	Nanoxel	2007	I 422122		N
paclitaxel nanoparticles	Genexol-PM	2007	I 811264		N
pentostatin	Nipent	1992	ARMC 28	334	N
peplomycin	Pepleo	1981	I 090889		N
romidepsin	Istodax	2010	DNP 23	18	N
trabectedin	Yondelis	2007	ARMC 43	492	N
solamargines	Curaderm	1989	DNP 03	25	NB
abiraterone acetate	Zytiga	2011	DT 48(1)	44	ND
alitretinoin	Panretin	1999	ARMC 35	333	ND
aminolevulinic Me ester	Metvix	2001	DNP 15	34	ND
amrubicin HCl	Calsed	2002	ARMC 38	349	ND
belotecan HCL	Camtobell	2004	ARMC 40	449	ND
bf-200 ala	Ameluz	2012	I 431098		ND
brentuximab vedotin	Adcetris	2011	DT 48(1)	45	ND
cabazitaxel	Jevtana	2010	I 287186		ND
carfilzomib	Kyprolis	2012	I 413092		ND
cladribine	Leustatin	1993	ARMC 29	335	ND
cytarabine ocfosfate	Starsaid	1993	ARMC 29	335	ND
docetaxel	Taxotere	1995	ARMC 31	341	ND
elliptinium acetate	Celiptium	1983	I 091123		ND
epirubicin HCI	Farmorubicin	1984	ARMC 20	318	ND
eribulin	Halaven	2010	I 287199		ND
etoposide phosphate	Etopophos	1996	DNP 10	13	ND
exemestane	Aromasin	1999	DNP 13	46	ND
formestane	Lentaron	1993	ARMC 29	337	ND
forodesine HCl	Mundesine	2017	DT 54	59	ND
fulvestrant	Faslodex	2002	ARMC 38	357	ND
gemtuzumab ozogamicin	Mylotarg	2000	DNP 14	23	ND
hexyl aminolevulinate	Hexvix	2004	I 300211		ND
idarubicin HCl	Zavedos	1990	ARMC 26	303	ND
inotuzumab ozogamicin	Besponsa	2017	MCR 53	634	ND
irinotecan HCl	Campto	1994	ARMC 30	301	ND
ixabepilone	Ixempra	2007	ARMC 43	473	ND
midostaurin	Rydapt	2017	MCR 53	644	ND
mifamurtide	Junovan	2010	DNP 23	18	ND
miltefosine	Miltex	1993	ARMC 29	340	ND
padeliporfin potassium	Stakel	2015	I 368226		ND
pirarubicin	Pinorubicin	1988	ARMC 24	309	ND
polatuzumab vedotin	Polivy	2019	I 728238		ND
pralatrexate	Folotyn	2009	DNP 23	18	ND
talaporfin sodium	Laserphyrin	2004	ARMC 40	469	ND
temsirolimus	Toricel	2007	ARMC 43	490	ND
topotecan HCl	Hycamptin	1996	ARMC 32	320	ND
trastuzumab emtansine	Kadcyla	2013	DT 50(1)	69	ND
triptorelin	Decapeptyl	1986	I 090485		ND
valrubicin	Valstar	1999	ARMC 35	350	ND
vapreotide acetate	Docrised	2004	I 135014		ND
vinflunine	Javlor	2010	I 219585		ND
vinorelbine	Navelbine	1989	ARMC 25	320	ND
zinostatin stimalamer	Smancs	1994	ARMC 30	313	ND
aminoglutethimide	Cytadren	1981	I 070408		S
amsacrine	Amsakrin	1987	ARMC 23	327	S
arsenic trioxide	Trisenox	2000	DNP 14	23	S
bisantrene HCl	Zantrene	1990	ARMC 26	300	S
carboplatin	Paraplatin	1986	ARMC 22	318	S
cobimetinib	Cotellic	2015	MCR 51	469	S
flutamide	Drogenil	1983	ARMC 19	318	S
fotemustine	Muphoran	1989	ARMC 25	313	S

https://dx.doi.org/10.1021/acs.jnatprod.9b01285
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Table 8. continued

generic name	trade name	year intro.	volume	page	source
heptaplatin/SK-2053R	Sunpla	1999	ARMC 35	348	S
lobaplatin	Lobaplatin	1998	DNP 12	35	S
lonidamine	Doridamina	1987	ARMC 23	337	S
miriplatin hydrate	Miripla	2010	DNP 23	17	S
nedaplatin	Aqupla	1995	ARMC 31	347	S
nilutamide	Anadron	1987	ARMC 23	338	S
olaparib	Lynparza	2014	DT 51(1)	56	S
oxaliplatin	Eloxatin	1996	ARMC 32	313	S
plerixafor HCl	Mozobil	2009	DNP 22	17	S
pomalidomide	Pomalyst	2013	DT 50(1)	70	S
porfimer sodium	Photofrin	1993	ARMC 29	343	S
ranimustine	Cymerine	1987	ARMC 23	341	S
rucaparib	Rubraca	2016	MCR 52	583	S
selinexor	Xpovio	2019	I 768270		S
sobuzoxane	Parazolin	1994	ARMC 30	310	S
sonidegib phosphate	Odomzo	2015	MCR 51	519	S
sorafenib	Nexavar	2005	DNP 19	45	S
talazoparib tosylate	Talzenna	2018	DT 55	59	S
venetoclax	Venclexta	2016	MCR 52	585	S
vismodegib	Erivedge	2012	I 473491		S
zoledronic acid	Zometa	2000	DNP 14	24	S
alectinib HCl	Alecensa	2014	DT 51(1)	54	S/NM
alpelisib	Piqray	2019	I 684507		S/NM
anastrozole	Arimidex	1995	ARMC 31	338	S/NM
apalutamide	Erleada	2018	DT 55	59	S/NM
apatinib mesylate		2014	DT 51(1)	56	S/NM
bicalutamide	Casodex	1995	ARMC 31	338	S/NM
binimetinib	Mektovi	2018	DT 55	61	S/NM
binimetinib	Mektovi	2018	I 349927		S/NM
bortezomib	Velcade	2003	ARMC 39	345	S/NM
camostat mesylate	Foipan	1985	ARMC 21	325	S/NM
ceritinib	Zykadia	2014	DT 51(1)	55	S/NM
chidamide	Epidaza	2015	MCR 51	467	S/NM
darolutamide	Nubeqa	2019	I 730297		S/NM
dasatinib	Sprycel	2006	DNP 20	27	S/NM
enasidenib mesylate	Idhifa	2017	MCR 53	627	S/NM
encorafenib	Braftovi	2018	DT 55	61	S/NM
enzalutamide	Xtandi	2012	I 438422		S/NM
erlotinib HCl	Tarceva	2004	ARMC 40	454	S/NM
fadrozole HCl	Afema	1995	ARMC 31	342	S/NM
gefitinib	Iressa	2002	ARMC 38	358	S/NM
glasdegib maleate	Daurismo	2018	DT 55	63	S/NM
imatinib mesilate	Gleevec	2001	DNP 15	38	S/NM
ivosidenib	Tibsovo	2018	DT 55	62	S/NM
ixazomib citrate	Ninlaro	2015	MCR 51	487	S/NM
lapatinib ditosylate	Tykerb	2007	ARMC 43	475	S/NM
letrazole	Femara	1996	ARMC 32	311	S/NM
lorlatinib	Lorbrena	2018	DT 55	61	S/NM
nilotinib HCl	Tasigna	2007	ARMC 43	480	S/NM
niraparib	Zejula	2017	MCR 53	651	S/NM
panobinostat lactate	Farydak	2015	MCR 51	507	S/NM
pazopanib	Votrient	2009	DNP 23	18	S/NM
pexidartinib	Turalio	2019	I 655649		S/NM
qizartinib	Vanflyta	2019	I 443269		S/NM
sunitinib malate	Sutent	2006	DNP 20	27	S/NM
temoporfin	Foscan	2002	I 158118		S/NM
toremifene	Fareston	1989	ARMC 25	319	S/NM
azacytidine	Vidaza	2004	ARMC 40	447	S*
capecitabine	Xeloda	1998	ARMC 34	319	S*
carmofur	Mifurol	1981	I 091100		S*
clofarabine	Clolar	2005	DNP 19	44	S*

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Table 8. continued

generic name	trade name	year intro.	volume	page	source
decitabine	Dacogen	2006	DNP 20	27	S*
doxifluridine	Furtulon	1987	ARMC 23	332	S*
enocitabine	Sunrabin	1983	ARMC 19	318	S*
fludarabine phosphate	Fludara	1991	ARMC 27	327	S*
gemcitabine HCl	Gemzar	1995	ARMC 31	344	S*
mitoxantrone HCI	Novantrone	1984	ARMC 20	321	S*
nelarabine	Arranon	2006	ARMC 42	528	S*
pixantrone dimaleate	Pixuri	2012	I 197776		S*
tipiracil HCl	Lonsurf	2014	DT 51(1)	58	S*
abarelix	Plenaxis	2004	ARMC 40	446	S*/NM
abemaciclib mesylate	Verzenio	2017	MCR 53	595	S*/NM
acalabrutinib	Calquence	2017	MCR 53	595	S*/NM
afatinib	Gilotrif	2013	DT 50(1)	69	S*/NM
axitinib	Inlyta	2012	I 318296		S*/NM
belinostat	Beleodaq	2014	DT 51(1)	56	S*/NM
bexarotene	Targretine	2000	DNP 14	23	S*/NM
bosutiniib	Bosulif	2012	I 301966		S*/NM
brigatinib	Alunbrig	2017	MCR 53	610	S*/NM
cabozantinib *S*-malate	Cometriq	2012	I 379934		S*/NM
copanlisib	Aliqopa	2017	MCR 53	614	S*/NM
crizotinib	Xalkori	2011	DT 48(1)	45	S*/NM
dabrafenib mesilate	Tafinlar	2013	DT 50(1)	69	S*/NM
dacomitinib	Vizimpro	2018	DT 55	61	S*/NM
degarelix	Firmagon	2009	DNP 22	16	S*/NM
duvelisib	Copiktra	2018	DT 55	62	S*/NM
entrectinib	Rozlytrek	2019	I 653437		S*/NM
erdafitinib	Balversa	2019	I 790489		S*/NM
fedratinib HCl	Inrebic	2019	I 441519		S*/NM
fruquintinib	Elunate	2018	DT 55	61	S*/NM
gilteritinib	Xospata	2018	DT 55	62	S*/NM
ibrutinib	Imbruvica	2013	DT 50(1)	71	S*/NM
idelalisib	Zydelig	2014	DT 51(1)	54	S*/NM
ivosidenib	Tibsovo	2018	I 833473		S*/NM
larotrectinib sulfate	Vitrakvi	2018	DT 55	59	S*/NM
lenvatinib mesylate	Lenvima	2015	MCR 51	489	S*/NM
neratinib	Nerlynx	2017	MCR 53	647	S*/NM
olmutinib	Olita	2016	MCR 52	574	S*/NM
osimertinib mesylate	Tagrisso	2015	MCR 51	502	S*/NM
palbociclib	Ibrance	2015	MCR 51	505	S*/NM
pemetrexed disodium	Alimta	2004	ARMC 40	463	S*/NM
ponatinib	Iclusig	2013	DT 50(1)	70	S*/NM
pyrotinib	Airuini	2018	DT 55	59	S*/NM
radotinib	Supect	2012	I 446133		S*/NM
raltiterxed	Tomudex	1996	ARMC 32	315	S*/NM
regorafenib	Stivarga	2012	I 395674		S*/NM
ribociclib	Kisqali	2017	MCR 53	660	S*/NM
ruxolitinib phosphate	Jakafi	2011	DT 48(1)	47	S*/NM
tamibarotene	Amnoid	2005	DNP 19	45	S*/NM
temozolomide	Temodal	1999	ARMC 35	350	S*/NM
tivozanib	Fotivda	2017	MCR 53	668	S*/NM
trametinib DMSO	Mekinist	2013	DT 50(1)	69	S*/NM
vandetanib	Caprelsa	2011	DT 48(1)	45	S*/NM
vemurafenib	Zeboraf	2011	DT 48(1)	45	S*/NM
vorinostat	Zolinza	2006	DNP 20	27	S*/NM
	Cervarix	2007	I 309201		V
	Apceden-CR	2017	DT 54	64	V
	Apceden-L	2017	DT 54	64	V
	Apceden-O	2017	DT 54	64	V
	Apceden-P	2017	DT 54	64	V
autol. tumor cell-BCG	OncoVAX	2008	DNP 22	17	V
bcg live	TheraCys	1990	DNP 04	104	V

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Table 8. continued

generic name	trade name	year intro.	volume	page	source
melanoma theraccine	Melacine	2001	DNP 15	38	V
talimogene laherparepvec	Imlygic	2015	DT 52	62	V
vitespen	Oncophage	2008	DNP 22	17	V

[a]If no generic name, then trade name given within source classification.

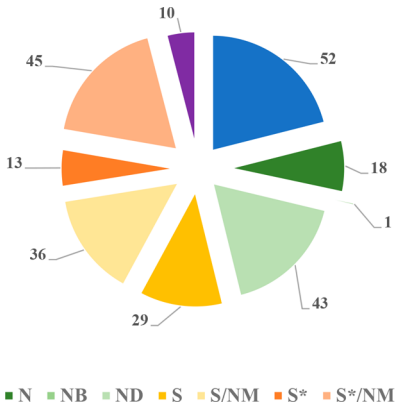

Figure 15. All anticancer drugs 01JAN81−30SEP19, n = 247.

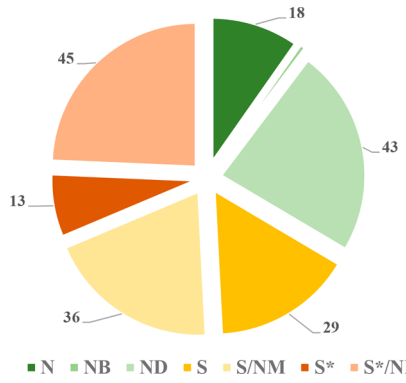

Figure 17. Small anticancer drugs 01JAN81−30SEP19, n = 185.

2019, the "V" component amounted to ∼47% of the 185 identified agents. Looking at small molecules there was one ND, tenofovir disoproxil (**20**), an orotate salt of a compound first approved as the fumarate in 2001. There were four single agents in the "S" category, two for HIV, one for CMV, and one for HSV1 (shingles potential). Very recently (mid-December 2019), the story of the non-nucleoside reverse transcriptase inhibitor (NNRTI) doravirine (**21**), designed to be active against the HIV reverse transcriptase, was initially published as an advance article in late 2019 in *ACS Infectious Diseases* by the Merck team involved.[123] These authors used the term "rational design", which was reasonable usage of the term, but it was not a de novo construct, since it started from a series of compounds based on MK-1107 (**22**) as shown in Table 1 in their paper. The combination of sofosbuvir (approved in 2013) and velpatasvir (**23**), which is currently in phase II clinical trials, was approved by the FDA for HCV treatment under the trade name Epclusa. This is a similar situation to those described earlier in the antibacterial section.

In the "S*" category, there were three "defined mixtures" two with three drug components and one with two. Again, approved single agents were "combined" in a fixed ratio with agents that were still in clinical trials for HCV treatment. In contrast, of the four drugs approved under the "S*/NM" category, only one, with the trade name of Maviret, is composed of a fixed ratio of two compounds that are individually in phase II trials (glecaprevir and pibrentasvir) and is approved for HCV treatment in adults. Of the others, Narlaprevir (**24**), which was launched in Russia in 2016, is for HCV treatment, and one of the two agents approved in China in 2018, danoprevir (**25**), is also for HCV treatment, with the other, albuvirtide, being a peptidic HIV fusion inhibitor.

In the "S/NM" category there were four approved agents. Grazoprevir is an inhibitor of the NS3/4A protease in HCV genotype 1, elbasvir is an inhibitor of the NS5A protease in HCV, baloxavir (**26**), on the other hand, is a cap-dependent endonuclease inhibitor in influenza A and B viruses, and the fourth, tecovirimat (**27**), is an inhibitor of the core protein cysteine proteinase in the pox virus 17L gene and is being stockpiled in the USA's strategic national stockpile.

Antiparasitic Drugs. Though we did not split out this section in our previous reviews, and the number of approved drugs since 1981 is low, with only 20 approved in the current time frame, the number of patients in the developing and in the poorer parts of the developed world is measured in very

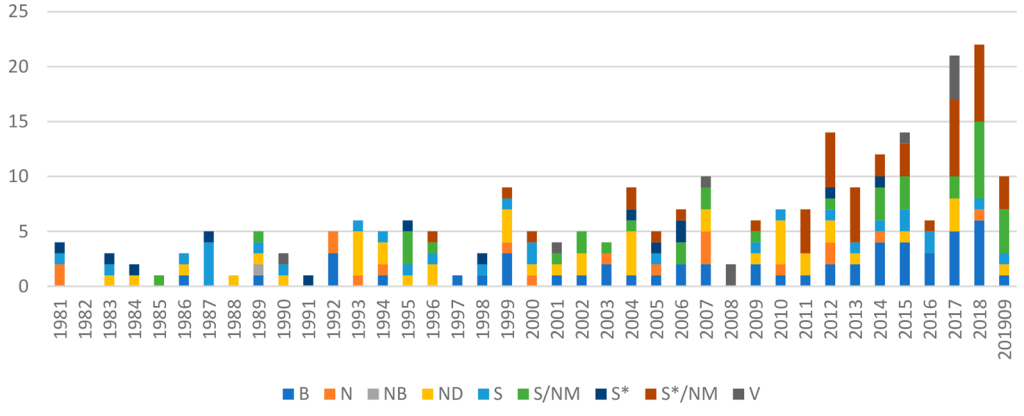

Figure 16. All anticancer drugs 01JAN81−30SEP19, n = 247 (bar chart).

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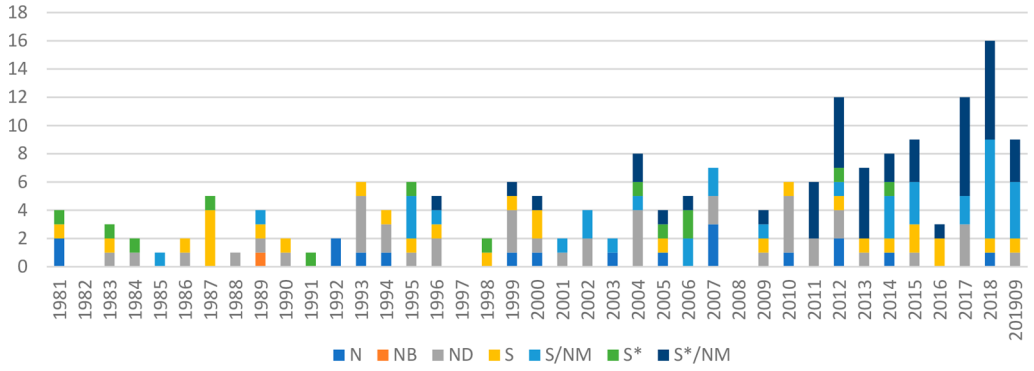

Figure 18. Small anticancer drugs 01JAN81−30SEP19, n = 185 (bar chart).

Table 9. Anticancer Drugs 1946 to 1980

generic name	year intro.	reference	page	source
carzinophilin	1954	Japan Antibiotics		N
sarkomycin	1954	Japan Antibiotics		N
chromomycin A3	1961	Japan Antibiotics		N
neocarzinostatin	1976	Japan Antibiotics		N
actinomycin D	1964	FDA		N
asparaginase	1969	FDA		N
bleomycin	1966	FDA		N
daunomycin	1967	FDA		N
doxorubicin	1966	FDA		N
leucovorin	1950	FDA		N
mithramycin	1961	FDA		N
mitomycin C	1956	FDA		N
neocarzinostatin	1976	Japan Antibiotics		N
streptozocin	pre-1977	Carter		N
testosterone	pre-1970	Carter		N
vinblastine	1965	FDA		N
vincristine	1963	FDA		N
calusterone	1973	FDA		ND
dexamethasone	1958	FDA		ND
dromostanolone	1961	FDA		ND
estramustine	1980	FDA		ND
ethinyl estradiol	pre-1970	Cole		ND
etoposide	1980	FDA		ND
fluoxymesterone	pre-1970	Cole		ND
fosfestrol	pre-1977	Carter		ND
hydroxprogesterone	pre-1970	Cole		ND
medroxyprogesterone acetate	1958	FDA		ND
megesterol acetate	1971	FDA		ND
methylprednisolone	1955	FDA		ND
methyltestosterone	1974	FDA		ND
mitobronitol	1979	FDA		ND
naldrolone phenylpropionate	1959	FDA		ND
norethindone acetate	pre-1977	Carter		ND
prednisolone	pre-1977	Carter		ND
prednisone	pre-1970	Cole		ND
teniposide	1967	FDA		ND
testolactone	1969	FDA		ND
triamcinolone	1958	FDA		ND
vindesine	1979	FDA		ND
busulfan	1954	FDA		S
carmustine	1977	FDA		S
chlorambucil	1956	FDA		S
chlortrianisene	pre-1981	Boyd		S
cis-diamminedichloroplatinum	1979	FDA		S
cyclophosphamide	1957	FDA		S
dacarbazine	1975	FDA		S
diethylstilbestrol	pre-1970	Cole		S
hexamethylmelamine	1979	FDA		S
hydroxyurea	1968	FDA		S
ifosfamide	1976	FDA		S
levamisole	pre-1981	Boyd		S
lomustine	1976	FDA		S
mechlorethanamine	1958	FDA		S
melphalan	1961	FDA		S
mitotane	1970	FDA		S
mustine HCl		M'dale 36	697	S
nimustine HCl	pre-1981	M'dale 36	756	S
pipobroman	1966	FDA		S
procarbazine	1969	FDA		S
razoxane	pre-1977	Carter		S
semustine	pre-1977	Carter		S
thiotepa	1959	FDA		S
triethylenemelamine	pre-1981	Boyd		S
nafoxidine	pre-1977	Carter		S/NM
tamoxifen	1973	FDA		S/NM
aminogluethimide	1980	FDA		S*
cytosine arabinoside	1969	FDA		S*
floxuridine	1971	FDA		S*
fluorouracil	1962	FDA		S*
ftorafur	1972	FDA		S*
mercaptopurine	1953	FDA		S*
methotrexate	1954	FDA		S*
thioguanine	1966	FDA		S*
uracil mustard	1966	FDA		S*

large numbers, with few people in the higher economic parts of the developed world fully realizing the very significant numbers of people affected by parasites, and frequently with more than one. Malaria is the parasitic disease best recognized by nonscientists in the West, with figures of over a million deaths/year due to malaria frequently mentioned when the continent of Africa is considered. What is usually ignored/or not recognized are the other manifold parasites that affect people

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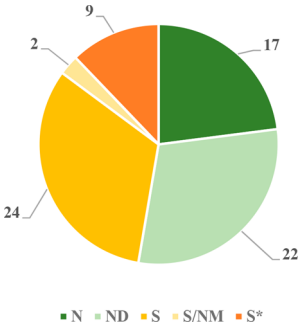
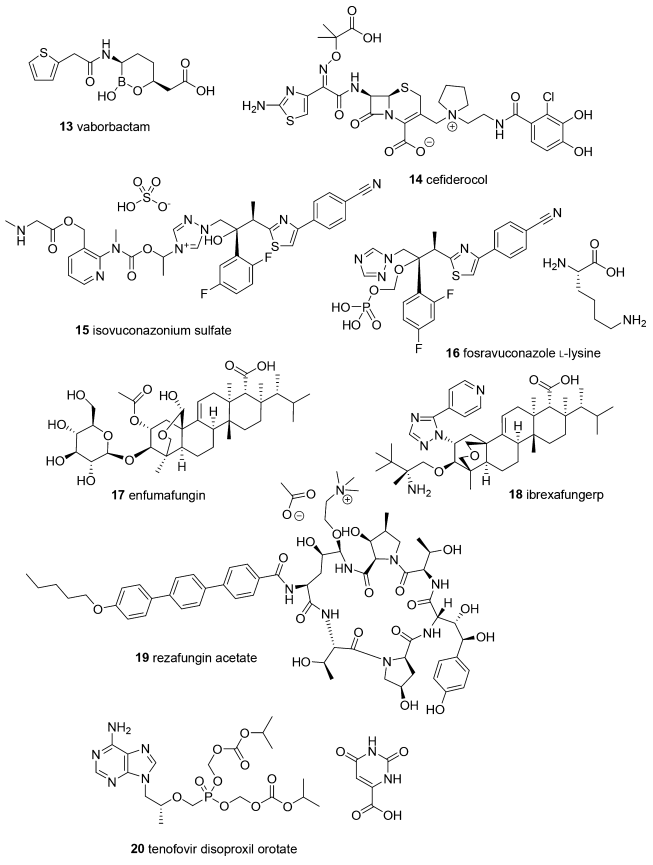
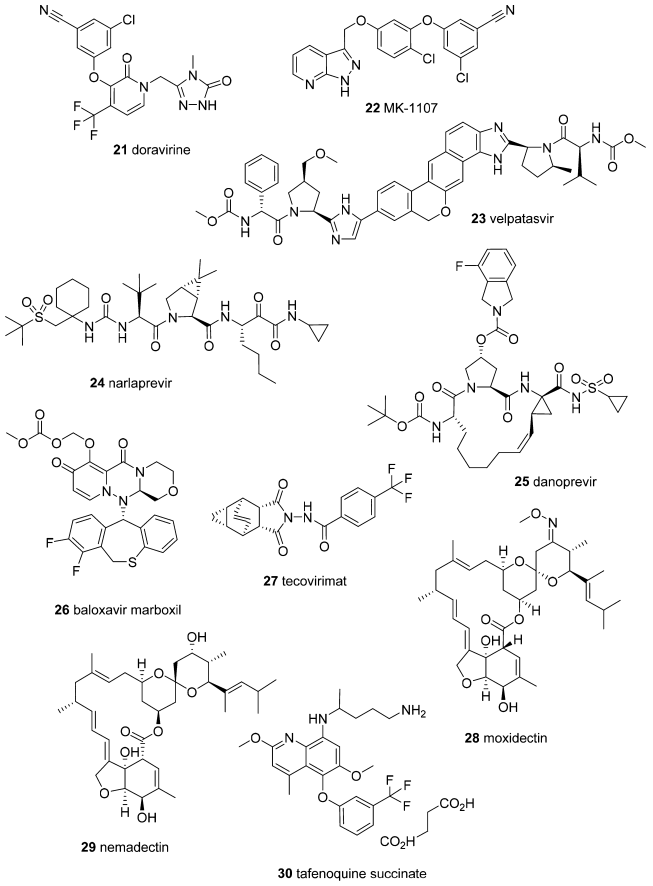


Figure 19. Anticancer drugs from 1946 to 1980, *n* = 74.



all over the world, in particular in tropical and subtropical areas of Asia and Central and South America in addition to Africa. A recent short review by Pisarski[124] puts the case for much more work to be done for other major parasitic diseases, in addition



to the work done against river blindness in Africa, which was recognized by the award of 50% of the 2015 Nobel Prize in Physiology or Medicine for the ivermectins.

The above commentary is significant, since in 2018 the milbemycin derivative moxidectin (**28**) was approved in the USA for human use. This molecule is a semisynthetic derivative of nemadectin (**29**), a naturally occurring milbemycin class molecule for which the full structure including the biosynthesis was published in 1989 by Tsou et al.;[125] thus moxidectin is an "ND". The same year, the prodrug tafenoquine succinate (**30**) was approved as an antimalarial agent and is also an "ND", similar in reasoning to chloroquine and others. A discussion of prodrugs including this agent is in the 2019 paper by Najer and Karaman, which makes interesting reading.[126] The totally synthetic compound fexindazole (**31**) was also approved in 2019 but this time for

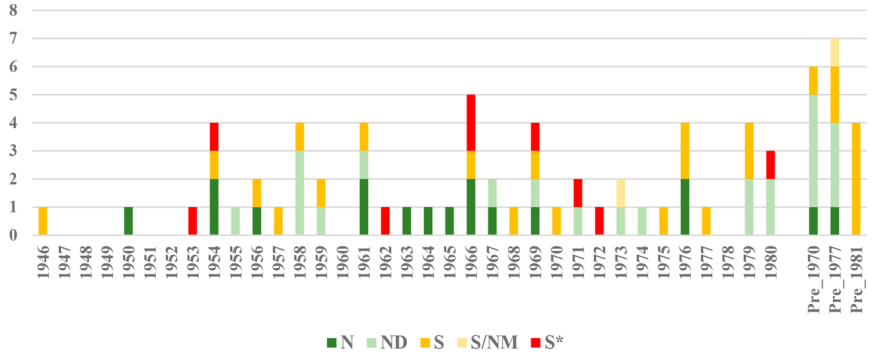


Figure 20. Anticancer drugs from 1946 to 1980 by year, *n* = 74 (bar chart).

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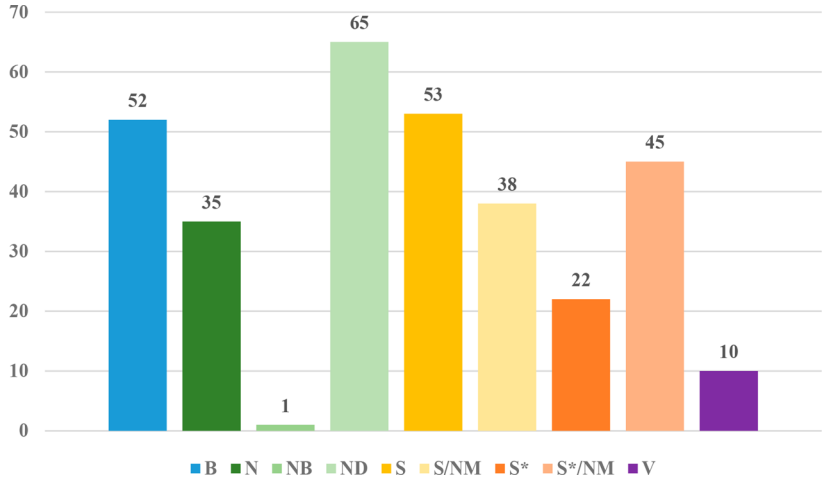
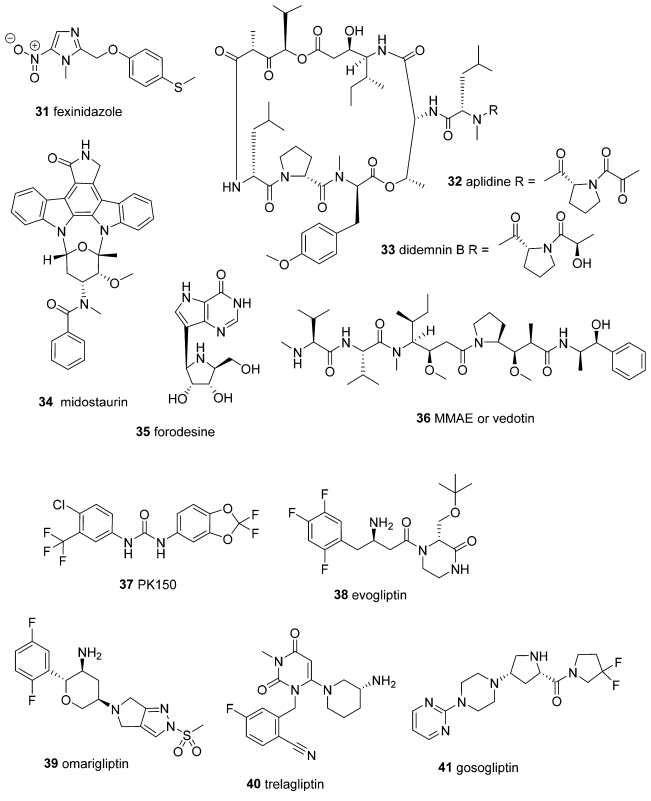


Figure 21. All anticancer drugs 1946−30SEP19, n = 321 (bar chart).

use against trypanosomiasis and is in clinical trials for Chagas' disease.

In 2018, Efferth reported on the "other" activities of artemisinin and derivatives. This review demonstrated that there was significant in vitro activity against a wide range of viruses, which would not be expected for an antimalarial agent.[127] This review is definitely worth reading, as it demonstrates that one needs to "think laterally" when considering what a given chemical class might be active against.



Overall Figures for Anti-infectives. Although the four major areas of anti-infective drugs were discussed individually in the sections above, in Table 7 we show the overall statistics for these agents so that the contributions of the "N*" and "S*" categories can be seen across the four broad areas, demonstrating that these categories account for 136 approved agents, or 52.7% of the total of 401 small molecules.

Antitumor Agents I (01JAN1981−30SEP2019). As mentioned in the Introduction, we have split the antitumor drug listings into two sections in this review, those approved from 01JAN1981 to 30SEP2019 and the earlier approved drugs (1946 to the end of 1980), which will be discussed in the following section. This was done in order to avoid the significant duplication of the large tables in this section that occurred in our earlier reviews.

Inspection of Table 8 and Figures 15−18 shows that in the time frame covered (01/1981−09/2019) there were 247 NCEs in toto, with the number of nonbiologicals and vaccines, i.e., small molecules, being 185 (75%) and reasonably close to the figure of 78% in the last review, though one needs to consider that the previous reviews included data from the initial date of the middle 1930s, whereas this section of the current review does not.[5] Using the small-molecule total of 185 (Figures 17 and 18) as being equal to 100%, the breakdown for this analysis was as follows: N (18, 9.7%), NB (1, 0.5%), ND (43, 23.2%), S (29, 15.7%), S/NM (36, 19.5%), S* (13, 7%), S*/NM (45, 24%). Thus, using our criteria, only 29 (15.7%) of the total number of small-molecule anticancer drugs in this time period were classifiable into the S (totally synthetic) category. If we remove the "/NM" categories from the overall small-molecule listings but maintain the S* category, then the compounds that can be assignable to naturally inspired sources total 75, or 41%.

Though readers of our earlier reviews will almost certainly comment that we always quoted a figure of ∼60% in those reviews, it must be borne in mind that these are now figures for drugs from 1981. In the section in these analyses covering antitumor drugs from 1946 to 1980 we will show the corresponding figures from those data, together with the combined figures. The overall breakdown can be seen in Figures 15 to 18, where the contribution of each source can be seen as either pie charts or bar graphs, thus permitting readers to analyze the data as they desire.

Antitumor Agents in the N/S* Categories.* From a natural products perspective, in the antitumor area there were some significant approvals in the almost five years from 01JAN2015 to 30SEP2019. The unmodified marine natural product Aplidine (**32**) was finally approved in Australia at the end of 2018 for the treatment of multiple myeloma, after being rejected a few years earlier by the EMA for the same indication. This molecule differs from the first marine natural product to

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Table 10. Diabetes I and II Agents from 19810101 to 20190930, Organized Alphabetically by Generic Name within Source

generic name	trade name	year intro.	volume	page	source
biphasic porcine insulin	Pork Mixtard 30	1982	I 303034		B
isophane insulin	Humulin N	1982	I 091583		B
porcine isophane insulin	Pork Insulatard	1982	I 302757		B
human insulin Zn suspension	Humulin L	1985	I 302828		B
human insulin zinc suspension	Humulin Zn	1985	I 091584		B
soluble insulin	Velosulin BR	1986	I 091581		B
human neutral insulin	Novolin R	1991	I 182551		B
hu neutral insulin	Insuman	1992	I 255451		B
mecasermin	Somazon	1994	DNP 08	28	B
insulin lispro	Humalog	1996	ARMC 32	310	B
porcine neutral insulin	Pork Actrapid	1998	I 302749		B
insulin aspart	NovoRapid	1999	DNP 13	41	B
insulin glargine	Lantus	2000	DNP 14	19	B
insulin aspart/IA protamine	NovoMix 30	2001	DNP 15	34	B
insulin determir	Levemir	2004	DNP 18	27	B
insulin glulisine	Apidra	2005	DNP 19	39	B
oral insulin	Oral-lyn	2005	DNP 19	39	B
pulmonary insulin	Exubera	2006	DNP 20	23	B
insulin degludec/ insulin aspar	DegludecPlus	2012	I 419438		B
insulin degludec	Degludec	2012	I 470782		B
pulmonary insulin	Afrezza	2014	DT 51(1)	45	B
albiglutide	Eperzan	2014	DT 51(1)	45	B
dulaglutide	Trulicity	2014	DT 51(1)	45	B
technosphere/ insulin	Afrezza	2015	I 290070		B
voglibose	Basen	1994	ARMC 30	313	N
acarbose	Glucobay	1990	DNP 03	23	ND
miglitol	Diastabol	1998	ARMC 34	325	ND
extenatide	Byetta	2005	DNP 19	40	ND
triproamylin acetate	Normylin	2005	DNP 19	40	ND
liraglutide	Victoza	2009	DNP 23	13	ND
lixisenatide	Lyxumia	2013	DT 50(1)	60	ND
semaglutide	Ozempic	2017	DT 55	48	ND
PEG-loxenatide	Fulaimei	2019	I 854088		ND
glimepiride	Amaryl	1995	ARMC 31	344	S
repaglinide	Prandin	1998	ARMC 34	329	S
pioglitazone HCl	Actos	1999	ARMC 35	346	S
mitiglinide calcium hydrate	Glufast	2004	ARMC 40	460	S
tolrestat	Alredase	1989	ARMC 25	319	S/NM
epalrestat	Kinedak	1992	ARMC 28	330	S/NM
troglitazone	Rezulin	1997	ARMC 33	344	S/NM
rosiglitazone maleate	Avandia	1999	ARMC 35	348	S/NM
sitagliptin	Januvia	2006	DNP 20	23	S/NM
vildagliptin	Galvus	2007	ARMC 43	494	S/NM
saxagliptin	Onglyza	2009	DNP 23	13	S/NM
alogliptin benzoate	Nesina	2010	I 405286		S/NM
linagliptin	Tradjenta	2011	DT 48(1)	39	S/NM
teneligliptin HBr	Tenelia	2012	I 343981		S/NM
anagliptin	Suiny	2012	I 426247		S/NM
gemiglptin	Zemiglo	2012	I 628733		S/NM
evogliptin HCl	Suganon	2015	MCR 52	555	S/NM
omarigliptin	Marizev	2015	MCR 51	500	S/NM
trelagliptin succinate	Zafatek	2015	DT 52	52	S/NM
gosogliptin HCl	SatRx	2016	MCR 52	557	S/NM
nateglinide	Starsis	1999	ARMC 35	344	S*
dapagliflozin	Forxiga	2012	I 356099		S*/NM
canagliflozin	Invokana	2013	DT 50(1)	60	S*/NM
empagliflozin	Jardiance	2014	DT 51(1)	45	S*/NM
ipragliflozin proline	Suglat	2014	DT 51(1)	45	S*/NM
tofogliflozin	Apleway	2014	DT 51(1)	45	S*/NM
luseogliflozin	Lusefi	2014	DT 51(1)	45	S*/NM
ertugliflozin	Steglatro	2017	MCR 53	628	S*/NM
sotagliflozin	Zynquista	2019	I 636286		S*/NM
remogliflozin etaborate	Remo	2019	I 324322		S*/NM

enter antitumor clinical trials, didemnin B (**33**), by the oxidation of the lactyl group on the pendant side chain in aplidine to give the diketo derivative didemnin B. Under the "ND" category, there were five agents approved with a porphyrin derivative in 2015, but more interestingly the first staurosporine derivative to be approved as a drug, midostaurin (**34**), was approved by the FDA as an *flt3* inhibitor in 2017, close to 25 years after its synthesis in a simple process.[128,129] Another rather old compound, now known as forodesine but originally synthesized under the name immucillin H (**35**), a simple variation on inosine and designed to mimic the transition state, was also approved in 2017.[130] In 2017, the second antibody−drug conjugate (ADC) using the same warhead as Mylotarg, a derivative of calicheamicin, was approved as inotuzumab ozogamicin. Finally, to round out the five NDs in the middle of 2019, a second ADC using the monomethylauristatin (MMAE) warhead (**36**) from Seattle Genetics was approved as polatuzumab vedotin. Although no S* molecules were approved in this time frame, 21 kinase inhibitors assignable to the S*/NM category were approved, three in 2015, one in 2016, eight in 2017, seven in 2018, and three in the first nine months of 2019. Their generic and trade names can be seen in Table 8 by using the year/S*/NM combination. There were also 17 small molecules in the same time frame that fell into the S/NM category, of which some were also protein kinase active agents.

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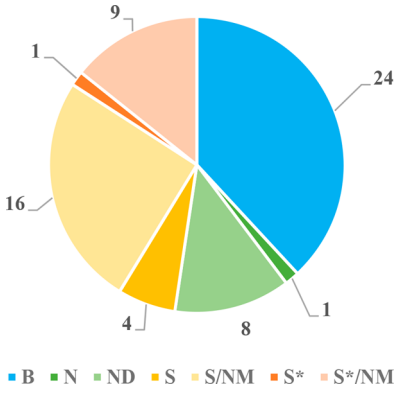

Figure 22. All antidiabetic drugs 01JAN81−30SEP19, n = 63.

Table 11. Multiple Sclerosis Agents from 01JAN1981 to 30SEP2019, Organized Alphabetically by Generic Name within Source

generic name	trade name	year intro.	volume	page	source
interferon, b-1b	Betaseron	1993	ARMC 29	339	B
interferon, beta-1a	Avonex	1996	ARMC 32	311	B
natalizumab	Tysabri	2004	ARMC 40	462	B
peginterferon beta-1a	Plegridy	2014	DT 51(1)	40	B
ocrelizumab	Ocrevus	2017	MCR 53	653	B
fingolimod HCl	Gilenya	2010	I 210392		ND
dimethyl fumarate	Tecfidera	2013	DT 50(1)	54	ND
monomethyl fumarate	Bafiertam	2019	I 384408		ND
siponimod fumarate	Mayzent	2019	I 389589		ND
4-aminopyridine	Ampyra	2010	I 182600		S
ataluren	Translarna	2014	DT 51(1)	51	S
glatiramer acetate	Copaxone	1997	ARMC 33	334	S*
teriflunomide	Aubagio	2012	I 178777		S*/NM

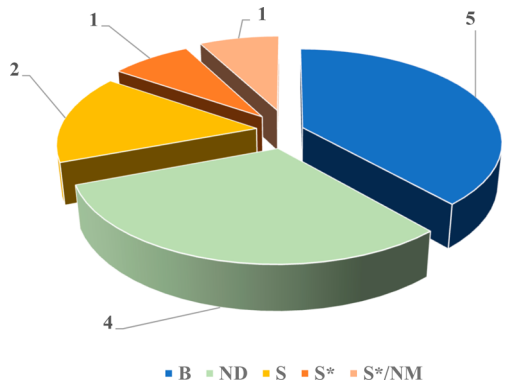

Figure 23. All multiple sclerosis drugs 01JAN81−30SEP19, n = 13.

Repurposing of an Approved Antitumor Kinase Inhibitor as a Potential Gram-Positive Antibiotic. Interestingly, the first approved drug that we were able to identify as a *de novo* combinatorial agent back in the 2007 review,[3] sorafenib (Nexavar; **3**), has become the starting structure in a very recent paper in *Nature Chemistry* that was first published on the Web on 19DEC2019.[131] That repurposing has led to the structure known as PK150 (**37**), where the right-hand side of sorafenib has been replaced by a five-membered dioxo ring, with a

Table 12. Antiglaucoma Agents from 01JAN1981 to 30SEP2019, Organized Alphabetically by Generic Name within Source

generic name	trade name	year intro.	volume	page	source
cenegermin	Oxervate	2017	DT 54	64	B
unoprostone isopropyl ester	Rescula	1994	ARMC 30	312	ND
latanoprost	Xalatan	1996	ARMC 32	311	ND
bimatoprost	Lumigan	2001	DNP 15	38	ND
travoprost	Travatan	2001	DNP 15	38	ND
tafluprost	Taflotan	2008	DNP 22	17	ND
latanoprostene bunod	Vyzulta	2017	MCR 53	637	ND
ripasudil HCl	Glanatec	2014	DT 51(1)	58	S
netarsudil mesylate	Rhopressa	2017	DT 54	64	S
dapiprazole HCl	Glamidolo	1987	ARMC 23	332	S/NM
apraclonidine HCl	Lopidine	1988	ARMC 24	297	S/NM
dorzolamide HCl	Trusopt	1995	ARMC 31	341	S/NM
brimonidine	Alphagan	1996	ARMC 32	306	S/NM
brinzolamide	Azopt	1998	ARMC 34	318	S/NM
omidenepag isopropyl	Eybelis	2018	DT 55	64	S/NM
befunolol HCI	Bentox	1983	ARMC 19	315	S*
carteolol HCl	Teoptic	1982	I 091513		S*/NM
methypranolol	Minims metipranolol	1982	I 317662		S*/NM
levobunolol HCI	Betagan	1985	ARMC 21	328	S*/NM

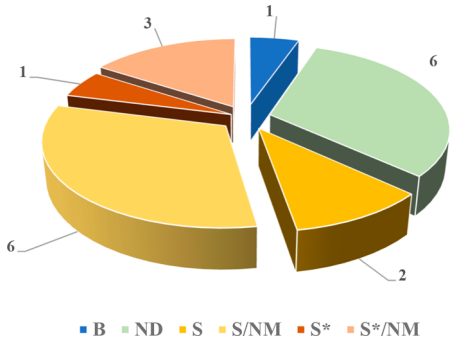

Figure 24. Antiglaucoma drugs 01JAN81−30SEP19, n = 19.

required difluoro substitution between the oxygen atoms in place of the pendant substituted pyridine in sorafenib. This compound (**37**) was more potent against *S. aureus* NCTC 8325 (MIC, 180 ng·mL^{-1}) when compared with vancomycin (MIC 1.4 μg·mL^{-1}) and linezolid (MIC 1.0 μg·mL^{-1}). There was also significant activity against various MRSA strains, and unlike sorafenib, it was also active against vancomycin-resistant *Enterococci* (MIC, 1.0 μg·mL^{-1}) and some mycobacteria, including *M. tuberculosis* (MIC, 0.93 μg·mL^{-1}). There was also indication of in vivo activity in murine models without obvious kidney toxicity (sorafenib is approved for renal cancer treatment). However, it was inactive against all Gram-negative bacteria tested.

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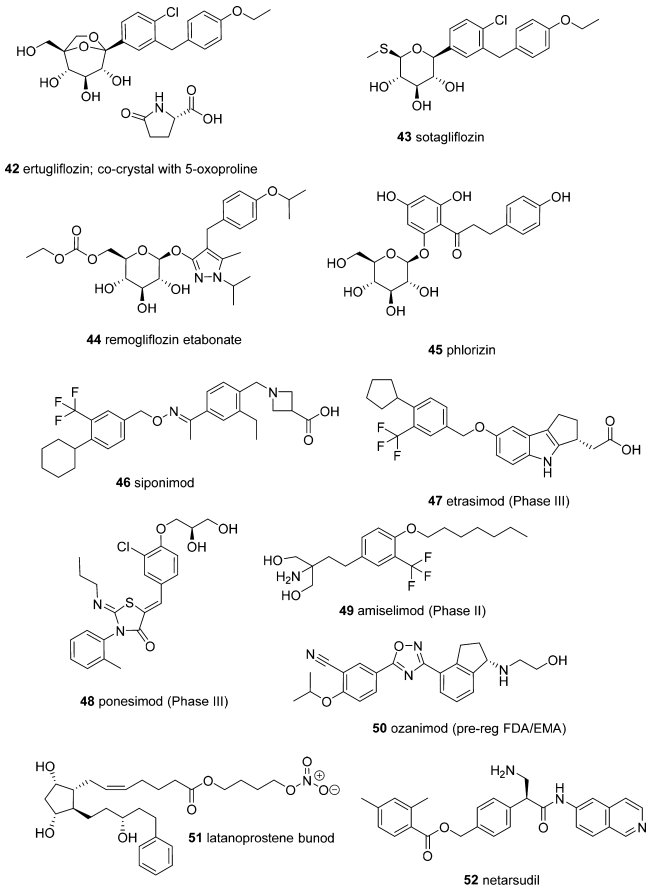
Table 13. Antibody Drug Conjugates in Phase II and III as of 27DEC2019

phase	generic name	warhead
II	anetumab ravtansine	DM-4
II	camidanlumab tesirine	PBD dimer
II	coltuximab ravtansine	DM-4
II	disitamab vedotin	MMAE
II	labetuzumab govitecan	SN-38
II	ladiratuzumab vedotin	MMAE
II	lifastuzumab vedotin	MMAE
II	loncastuximab tesirine	PBD dimer
II	lorvotuzumab mertansine	DM-1
II	naratuximab emtansine	DM-1
II	pinatuzumab vedotin	MMAE
II	PSMA-ADC	MMAE
II	telisotuzumab vedotin	MMAE
II	tisotumab vedotin	MMAE
III	BAT-8001	Maytansine derivative
III	mirvetuximab soravtansine	DM-4
III	trastuzumab duocarmazine	Seco-DUBA



Thus, a simple modification of sorafenib gave a compound that was 10-fold more active than the starting agent and had significant activity against resistant Gram-positive organisms, for which the target, *SpsB* (bacterial signal protease B), is the same as that of the arylomycins, compounds that are under early development in the pharmaceutical industry.[132−137] In contrast, however, PK150 "activates" the secretion of this enzyme, whereas the arylomycins "inhibit" the same target *SpSB*. It should also be pointed out that exhaustive studies did not demonstrate any kinase target in the bacterial cells.

Antitumor Agents II (1946−31DEC1980). As we mentioned in both the Introduction and the section above, we have analyzed the data on antitumor drugs prior to January 1981 as a separate section. We moved the date of first usage of the nitrogen mustards to 1946, from discussions in the second edition of the textbook on human pharmacology by Goodman and Gilman, which pointed to 1946 as being the most probable year for formal usage of these agents.[138] Then, using data from the FDA listings of antitumor drugs, plus help from Japanese colleagues, together with the literature resources referred to below, we have now been able to specify the years in which all but 17 of the 74 drugs listed in Table 9 were approved. Approximate date ranges for these 17 agents were derived by inspection of three time-relevant textbooks/compendia on antitumor treatment,[115,116,118] and these were added to the overall listings using the lead authors' names as the source citation. We should re-emphasize that there is no overlap between these 17 compounds and those for which we could find direct citations; thus they are legitimately approved compounds under the generic names used. As can be seen from Table 9 and Figures 19 and 20, the category counts are as follows: "N" 17, or 18.9%; "ND" 22, or 29.7%; and "S*" 9, or 12.2%, for a total of 48, or 64.8%.

Sources of All Approved Antitumor Drugs from 1946. If the figures from the two time periods reviewed above are now summed and plotted as a bar graph, then the resultant data may be shown in Figure 21. The total number of small antitumor molecules over the complete time frame comes to 259, with the "N" category accounting for 35, or 13.5%, the NB for 1, or 0.4%, and the "ND" category for 65, or 25.1%, and including the materials "inspired at one level or another by natural product structures", the S*, S*/NM, and S/NM categories, as we have done in previous reviews from 2003 onward, then we add another 105 compounds, giving a total of 206 for all low molecular weight categories except for pure synthetics (the S category), yielding a figure of 79%. We did not remove the sole NB compound, as this is a defined mixture of three low molecular weight solamargines. This number is slightly larger than the ∼77% in our 2016 review and is due mainly to the large number of kinase inhibitors that have been approved from 2015.

Antidiabetic Drugs. In the case of the antidiabetic drugs and considering only small molecules (now listed under the designation diabetes), the numbers total 39 with two "ND", four "S/NM", and three "S*/NM", nine more than identified in our 2016 review (Table 10). Semaglutide, which was approved in 2017, is an ND classification, as it, like extenatide (Byetta), is a derivative of Exendin-4.[139] It should also be noted that by use of clever pharmaceutics an oral preparation of this agent was approved in 2019 by the Chinese FDA. However, since this is the same product and not a chemical variation, we do not count it as a separate item. The other ND, PEG-loxenatide, is also a variation on extenatide, but this time with a polyethylene glycol "tail" attached via a maleimide link to the amidated carboxylate end. The data demonstrating a half-life of almost 6 days were published by Chinese investigators in 2015.[140] Neither of these two agents have their structures shown, as they are too large to fit under the restrictions for the journal. Under the classification S/NM, as mentioned above, there were four approvals of drugs that were targeted toward the same enzyme complex, dipeptidyl peptidase IV (DPP-IV). Of the four, three were approved in 2015, with the first in alphabetical order being evogliptin (**38**),

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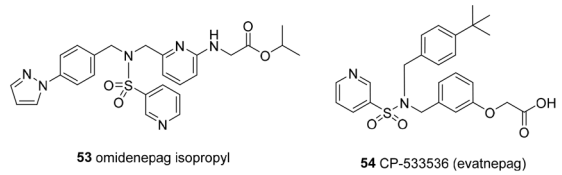
which was approved in 2015 in South Korea. This molecule was reported to have a unique binding mode with DPP4 in a 2017 paper by Lee et al.,[141] where the trifluorophenyl moiety fits in the S_1 pocket and the piperazine-2-one moiety has a hydrophobic interaction with Phe 257 in the S_2 site, which leads to further interactions with more amino acids, leading to a very potent agent. The second alphabetically was omarigliptin (**39**), which was developed by Merck and had its first launch in Japan. The synthesis of this agent was described in detail in 2017 by scientists from WuXi and makes interesting reading as to the use of a "one-pot" system at one stage, which when coupled to a crystallization process gave excellent ee results.[142] The last of the 2015 agents in this category was trelagliptin (**40**), which was approved in Japan. It is a Takeda drug and has a long-enough half-life for once a week dosing. It is not a covalent inhibitor but a reversible, competitive, and slow-binding inhibitor with a "$t_{1/2}$ dissoc" of ∼30 min, but it has a noncovalent binding mode from X-ray diffraction data, though since this is a solid-phase result, the actual binding could be somewhat different.[143] The fourth agent in this category, gosogliptin (**41**), was originally the Pfizer compound PF 734200, but in 2010 it was licensed to a Russian company and was approved in Russia in 2016, with a paper describing a synthetic route to this molecule published in 2012.[144]

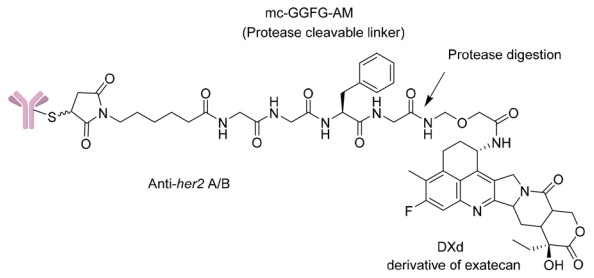
As was the case in the last review with this disease area, though the overall number was reduced from six to three, three more "flozins", targeted against the sodium-dependent glucose transporter (SGLT) and falling under the S*/NM classification, were approved by various authorities. The first, ertugliflozin (**44**), was approved by the FDA in 2017 as a cocrystal formulation with 5-oxo-proline and launched in the USA in 2018. The commercial route from 2,3,4,6-tetra-*O*-benzyl-D-glucose (commercially available) together with descriptions of the other methods/routes considered and/or attempted was published in 2014 by Bowles et al. from Pfizer,[145] and a short synthesis, though not on a commercial scale, starting from D-glucose was published by Triantakonstanti et al. in 2019.[146] In 2019, sotagliflozin (**43**) was approved in the EU as an adjunct oral therapy for adults with type I diabetes who could not achieve suitable glycemic control just using insulin. The third "flozin" in this classification was remogliflozin etaborate (**44**), which was approved in India in 2019 for the treatment of diabetes 2, though it was originated by Kissei in Japan and was in trials under GSK for use in diabetes 1 and 2. A 2018 publication in *Heterocycles* by scientists from Kissei gave the synthetic methods used.[147]

All of the agents in this class (SGLT-1/2 inhibitors) were based upon the nonselective natural product phlorizin (phloretin-2′-*O*-glucoside; **45**). The discovery of this agent with its potential for use in diabetes I was recently covered by Rendell in a 2019 review,[148] and the variations around structures such as these with SGLT2 activity were discussed in a recent review by Wang et al.[149] In addition to this review, the article in 2019 by Beitelshees et al. on the translational medicine aspect of these agents is also worth reading.[150]

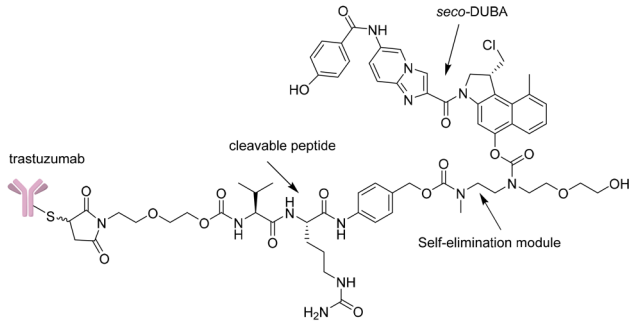
Multiple Sclerosis Agents. Inspection of Table 11 and Figure 23 shows that although the total numbers are low, two of the agents approved in 2019 were in the ND category. Interestingly, monomethyl fumarate was one, with its dimethyl analogue approved in 2013 and covered in our 2016 review. Of significant interest, however, was the approval of the fingolimod analogue siponomod fumarate (**46**) in 2019. Currently there are a number of other agents that are directed against the same targets as these two in current phase III clinical trials, etrasimod (**47**) and ponesimod (**48**), with another in phase II clinical trials, amiselimod (**49**), and one, ozanimod (**50**), which has been preregistered in both the USA (FDA) and the EU (EMA). To close out this section, in 2017, Dyckman published an excellent perspective in the *Journal of Medicinal Chemistry* that gave a thorough background on these agents and their derivation, which is well worth consulting.[151]



53 omidenepag isopropyl **54** CP-533536 (evatnepag)



55 trastuzumab deruxtecan



56 trastuzumab duocarmazine (SYD985)

Antiglaucoma Drugs. There were only three agents approved in this time period, all in 2017: the prostaglandin derivative latanoprostene bunod (**51**), classified as an ND, the S compound netarsudil mesylate (**52**), and the S/NM compound omidenepag isopropyl (**53**). What is of significant interest is that latanoprostene bunod is a prodrug of two agents with different mechanisms of action. On hydrolysis, this compound releases lananoprostic acid, which is a prostaglandin F2-α analogue, and butanediol mononitrate, which then undergoes further metabolism to nitric oxide, which leads to vascular relaxation. Together, they lead to lowering of the ocular pressure and thus relieve glaucoma. Two recent papers that cover this effect are the review by Imagnatiello et al. in 2018[152] and that by Najar and Karaman in 2019.[126] Also of interest is the review with a formal publication date of 2020 by Mehran et al. that covers the background of lanatoprostene bunod (**51**) and also the synthetic compound netarsudil (**52**).[153] What may be of greater import is that a fixed combination of these two agents was also approved by the FDA for glaucoma, but is not included in our data lists, as both agents are approved, rather than being fixed combinations of approved and unapproved (phase I to III) agents as in the

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cases discussed earlier under the antiviral and antimicrobial headings.

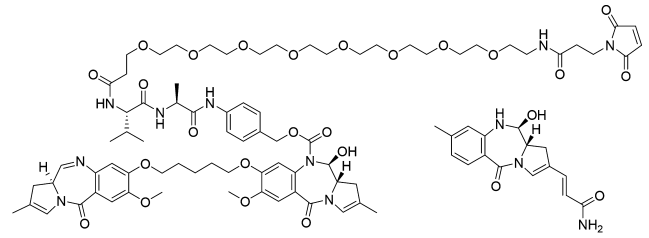
The third agent, omidenepag isopropyl (**53**), was approved in Japan for glaucoma. The origin of this nonprostanoid EP2 (prostaglandin E_2, or EP2) analogue was thoroughly discussed by Iwarmura et al. from Ube Industries in a 2018 paper in the *Journal of Medicinal Chemistry*.[154] The final compound was derived from an earlier Pfizer agent, CP-533536 (**54**), first reported by Cameron et al. in 2009,[155] with the full details of how this earlier compound, itself an EP_2 agonist, but being developed for bone regeneration, was subsequently developed by clever chemistry to yield omidenepag isopropyl.[154] This compound is also a prodrug, as it is hydrolyzed in the corneal epithelium to give the free acid that is the active agent.[152]

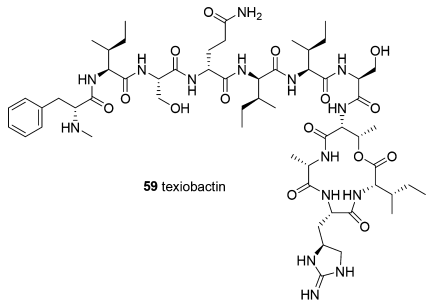
Although the "yield" of compounds in this area in the five years since our last review appears to be low, the three compounds discussed above demonstrate how inspired chemistry can lead to very potent and necessary compounds to treat glaucoma without the side effects that have been seen in earlier agents.

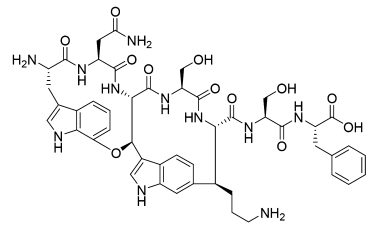
Discussion on Antibody–Drug Conjugates. As mentioned in the Introduction, a current major source of "warheads" for current and future ADCs is slight variations on natural products, with most of the current agents, be they already approved, in phase II or III clinical trials, being based upon what we now know to be microbial natural products. The progenitors of the warheads for approved, or for ADCs in phase II and III trials, with the one exception discussed later, were "derived" from the microbial products calicheamicin, maytansine, dolastatin 10, and duocarmycin. The current outliers in this regard are the warheads designed around camptothecin, though even in this case there are reports that endophytic microbes, including a *Bacillus* species with a required plasmid,[8] may be involved in addition to other endophytic fungal sources reported to yield camptothecin on fermentation.[25]

As of the end of the period of this review and looking at approved drugs, there were two ADCs with calicheamicin-derived warheads (Mylotarg, 2000; Besponsa, 2017), one maytansine derivative (Kadcyla, 2013), and two from the dolastatin 10 derivative monomethylauristatin E (**36**) (Adcetris, 2011; Polivy, 2019). Although not in the time frame, two more ADCs were approved by the FDA in December of 2019, with enfortumab vedotin (Padcev from Astellas and Seattle Genetics) approved on December 18, followed 2 days later by trastuzumab deruxtecan (Enhertu from Daiichi) on December 20. Neither of the December 2019 approvals have been included in the statistics in this review. The latter molecule has an interesting variation on the camptothecin basic structure known as deruxtecan as its warhead and is well described in a recent 2019 paper by Nakada et al.[156] In structure **55** we show the full linkage to the antibody and the mechanism(s) of release as described by the Nakada group.

Although there are numbers approaching 100 plus of ADCs in some form of testing from preclinical to phase III, in Table 13 we show the 14 phase II candidates and the three phase III candidates as of 27DEC2019. The structure of the warhead in the phase III candidate trastuzumab duocarmazine, which is also known as SYD-985, is shown in structure **56**, with the activation sequence also shown. Other pyrrolobenzodiazepine dimers use the name tesirine (**57**) as in the phase II candidate loncastuximab tesirine, when linked via varying cleavable or







noncleavable linkers to the antibody of choice, with all PBD derivatives being nominally based upon the microbial product anthramycin (**58**).[157] All of the other warheads have been discussed in published reviews.[12,18,158] The attrition rate of ADCs is quite high but not at the level of antibiotics or antitumor agents, where the success rate to approval from entering phase I is usually less than 10%.

Novel Antibiotics with Potential. As mentioned earlier in this review, very few antibiotics have been approved in the time frame covered, and one of the companies has already declared bankruptcy, less than a year after the approval of their aminoglycoside-based antibiotic. This was primarily due to not being able to sell enough to overcome the vast costs of approval. As mentioned in a lead article in the *New York Times* on 25DEC2019, there are at least two more small companies with approved antibiotics in a similar funding situation.

There are two interesting molecules that have been discovered by the Lewis group at Northeastern University in Boston, one from a few years ago, using a "baiting technique" loosely based on the "one-dose" concept that Diversa adopted from a collaborator. Using this "iChip" technique, the Lewis group reported on the peptide texiobactin (**59**), isolated from the previously unknown soil genus/species *Eleftheria terrae* and active against Gram-positive organisms. The initial report by Ling et al.[159] led to a significant number of papers covering potential mechanism(s) against Gram-positive microbes and also methods of synthesis, as fermentation would not be a viable production system. Recently, Zong et al. described in detail their methodology for large-scale synthesis, thus allowing a much easier access to this molecule.[160] The second molecule was also reported by the Lewis group and this time, from an analysis of the microbiome of the nematode Photorhabdus, yielding a molecule named darobactin (**60**). This molecule is

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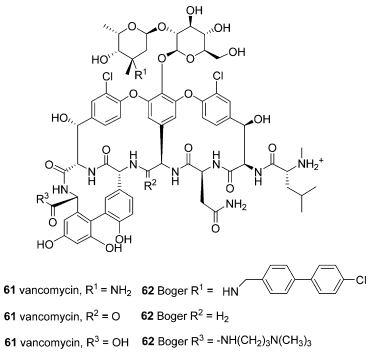
active against Gram-negative microbes, and apparently the mechanism of action involves BamA, an essential chaperone that folds outer membrane proteins.[161]



To finish this section, the number of Gram-positive microbial isolates that are now resistant to vancomycin are very high due to the presence of a number of resistance determinants. Rather than look for new antibiotics, a synthetic chemistry group at the Scripps Research Institute led by Boger decided to synthesize vancomycin from scratch, but in the process add in some "portions" of later approved glycopeptides with similar mechanisms of action, followed by making what appeared to be a very minor change in the peptide portion of the molecule, the conversion of an amide bond ketone to a methylene group. This synthetic "tour de force" yielded a totally synthetic molecule based on vancomycin that now was active against microbes with the vanR determinants. The structure of the base vancomycin (**61**) is given below with Boger's synthetic vancomycin structure (**62**), for comparison. The whole story was given in a condensed form in two 2018 papers that demonstrate the excellent work performed by the Boger group over the past few years on this topic.[21,22]

CONCLUSIONS

Though the number of groups actively working on natural products as drug leads has decreased to a very few in the pharmaceutical industry, and governmental funding for collection programs has effectively ceased in the USA and to some extent in other developed countries, the "influence of natural product structures" has not decreased materially over the last five years insofar as drug approvals that are based upon such structures are concerned. One only has to look at the source breakdowns in the pie charts and tables in this review to see that this is still a true statement except in one essential area.

As has been mentioned a "few times" both directly and indirectly, the outlook for novel antibiotics is not good, and that is a major understatement! Until some form of central support for antibiotic discovery and most importantly development can be established, then the dismal tone of the *New York Times* article referred to earlier will continue. Some form of accelerated development is necessary in this field, as there are now microbial resistance determinants in bacteria that have moved into man, for which there are no effective antibiotics. Although excellent work, as exemplified by the Lewis and Boger groups, plus others in this field, will continue to identify novel and potent agents, their development may well come to a full stop under the current funding systems. This is due to the developmental costs (quoted anywhere from around 0.5 to >1 billion U.S. dollars), and until these can be "adjusted" by the regulatory and/or other governmental agencies, then this area of drug discovery and development will "wither on the vine".

The large pharmaceutical industries realized a significant number of years ago that the "continuing costs" that had to be met if active programs directed against microbial and fungal diseases continued could not be met by the return on investment, under the current systems, to the extent that there are very few any size pharmaceutical companies still actively seeking these agents from natural sources. Perhaps it should also be commented on that although the public knows about the problems with antibacterial discovery, the problems with antifungal drug discovery are even more acute. There have been no new natural product-related antifungal agents since 2006; all the new agents are effectively based upon old azole chemistry, whereas new infective fungi are now being discovered in patients. We did show that there might be some agents in clinical trials against infectious fungi that are using materials derived from natural products, but how far they will go before funding becomes the problem is unknown, though infections with *Candida auris* are increasing with resistance to fluconazole, the echinocandins (with resistance being established on treatment), and even amphotericin B in about 30% of clinical isolates (2019 current data from the Centers for Disease Control).

Thus, as we have said several times in these reviews, natural products still hold out the best options for finding novel agents/active templates, which when worked on in conjunction with synthetic chemists and biologists, offer the potential to discover novel structures that can lead to effective agents in a variety of human diseases.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jnatprod.9b01285.

Information on the 1881 compounds (names, year, disease, codes) (PDF)

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Notes

The authors declare no competing financial interest.

DEDICATION

Dedicated to Dr. Jon Clardy of the Harvard Medical School for his pioneering work on Natural Products.

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