JOURNAL OF NATURAL PRODUCTS

Review

pubs.acs.org/jnp

Natural Products as Sources of New Drugs from 1981 to 2014

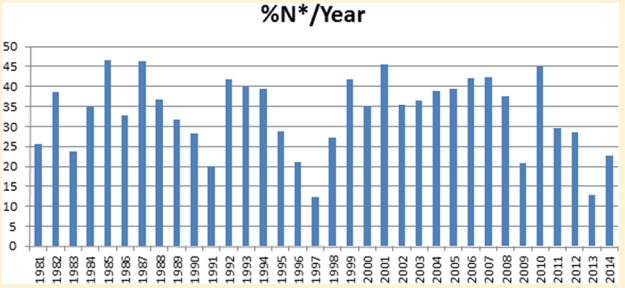
David J. Newman*,† and Gordon M. Cragg‡

†NIH Special Volunteer, Wayne, Pennsylvania 19087, United States

‡NIH Special Volunteer, Bethesda, Maryland 20814, United States

Supporting Information

ABSTRACT: This contribution is a completely updated and expanded version of the four prior analogous reviews that were published in this journal in 1997, 2003, 2007, and 2012. In the case of all approved therapeutic agents, the time frame has been extended to cover the 34 years from January 1, 1981, to December 31, 2014, for all diseases worldwide, and from 1950 (earliest so far identified) to December 2014 for all approved antitumor drugs worldwide. As mentioned in the 2012 review, 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 U.S. FDA (and similar organizations). From the data presented in this review, the utilization of natural products and/or 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 around the 1940s to the end of 2014, of the 175 small molecules approved, 131, or 75%, are other than "S" (synthetic), with 85, or 49%, actually being either natural products or directly derived therefrom. In other areas, the influence of natural product structures is quite marked, with, as expected from prior information, the anti-infective area being dependent on natural products and their structures. We wish to draw the attention of readers to the rapidly evolving recognition that a significant number of natural product drugs/leads are actually produced by microbes and/or microbial interactions with the "host from whence it was isolated", and therefore it is considered that this area of natural product research should be expanded significantly.



INTRODUCTION

It is now 18 years since the publication of our first review covering drugs from 1984 to 1995;[1] 12 years since the second, which covered the period from 1981 to 2002;[2] eight years since our third, covering the period 1981 to the middle of 2006;[3] and four years[4] since our last full analysis (covering the period 1981 to 2010), of the sources of new and approved drugs for the treatment of human diseases. In the present review we have also covered the four years from the beginning of 2011 to the end of 2014. In the last four years we have also published intermediate reports on natural products as leads to potential drugs,[5] the sources of antitumor compounds,[6] a general discussion on bioactive macrocycles from Nature,[7] an e-book series on natural products from microbial sources,[8−10] and a very recent book chapter on natural products in medicinal chemistry.[11] All of these articles have emphasized that natural product and/or natural product structures continue to play a highly significant role in the drug discovery and development process.

In Table 1, we have shown the genesis of our category codes and the years that we started with them. This is for the benefit of readers who are not familiar with these definitions and their derivation. The detailed reasoning behind the subgroup definition is given later under results.

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 34 years of data from 1981 to 2014 the system has been able to be refined. We have eliminated some duplicated entries that crept into the original data sets and have continued to revise some source designations, as newer information has been obtained from diverse sources. In particular, as behooves authors originally from the National Cancer Institute (NCI), in the specific case of cancer treatments, we have continued to consult the records of the U.S. FDA and have added comments from investigators who

Table 1. Codes Used in Analyses

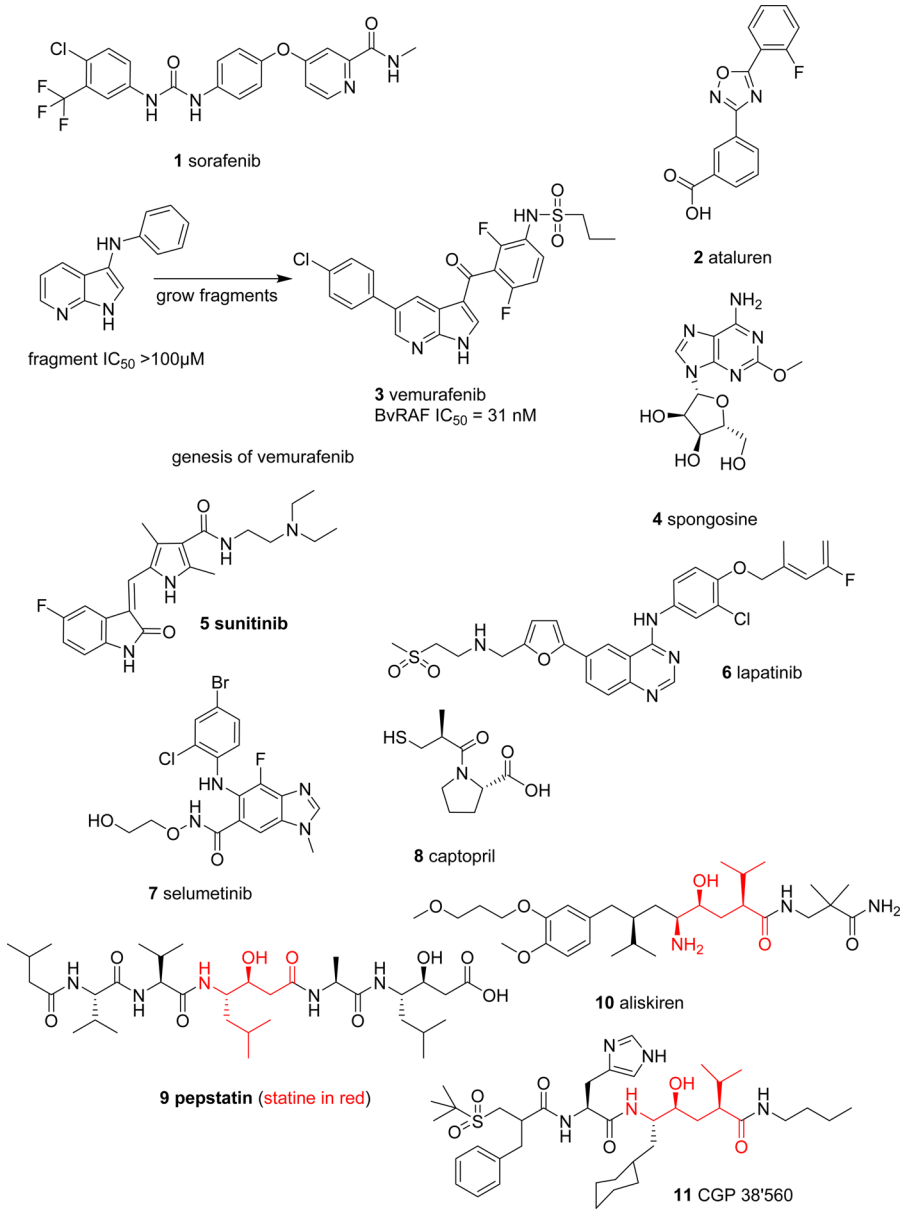
code	brief definition/year
B	Biological macromolecule, 1997
N	Unaltered natural product, 1997
NB	Botanical drug (defined mixture), 2012
ND	Natural product derivative, 1997
S	Synthetic drug, 1997
S*	Synthetic drug (NP pharmacophore), 1997
V	Vaccine, 2003
/NM	Mimic of natural product, 2003

Special Issue: Special Issue in Honor of John Blunt and Murray Munro

Received: November 27, 2015
Published: February 7, 2016

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Chart 1



have informed us of compounds that may have been approved in other countries and that were not included in our earlier searches. As was done previously, the cancer data will be presented as a stand-alone section from the beginning of formal chemotherapy in the very late 1930s or early 1940s to the present, but information from the last 34 years will be included in the data sets used in the overall discussion.

A trend mentioned in our 2003 review,[2] namely, the development of high-throughput screens based on molecular targets, had led to a demand for the generation of large libraries of compounds; however, the shift away from large combinatorial libraries that was becoming obvious at that time has continued even today, with the emphasis continuing to be on small focused (100−3000 plus) collections that contain much of the "structural aspects" of natural products. As mentioned in our 2012 review,[4] various names have been given to this process, including "diversity oriented syntheses",[12−16] but we prefer to refer simply to "more natural-product-like", in terms of their combinations of heteroatoms and significant numbers of chiral centers within a single molecule,[17] or even "natural product mimics" if they happen to be direct competitive inhibitors of the natural substrate (the origin of our subset listed as "?/NM"). It should also be pointed out, yet again, that 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".[18−20] An excellent paper by Koehn in 2012 gives a listing in Table 1 in that article of 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.[21] This paper together with one from Sweden by Doak et al.[22] and a very recent contribution by Camp et al.[23] should be part of any discussion on this aspect of natural product drugs.

Commentaries on the "industrial" perspective in regard to drug sources and high-throughput screening were published by the GSK group[24] in 2011, and very recently an intriguing article on what has been called "high throughput screening-dark chemical matter" (HTS-DCM) has opened the discussion on

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

molecules, some of which are based on natural products, that show no activities in in vitro assays but a number of which have very close structural analogues that are active.[25,26] These papers, the first of which is a perspective on the second much larger paper, should also be read in conjunction with a recent paper showing the natural product compound equivalents (invalid metabolic panaceas (IMPS))[27] to the pan-assay interference compounds (PAINS) that cause major problems in HTS programs.[28,29]

Although combinatorial chemistry in one or more of its manifestations has now been present as a discovery source for approximately 80% of the time covered by this review, to date, we still can only find one formal *de novo* new chemical entity reported in the public domain, with a second possibility discovered in a similar manner, with both approved for drug use. The first was the antitumor compound known as sorafenib (Nexavar, **1**) from Bayer, approved by the FDA in 2005 for treatment of renal cell carcinoma, and then in 2007, another approval was given for treatment of hepatocellular carcinoma. It has been approved in more than 100 countries as of the middle of 2014 for these two indications, and in late 2013, the U.S. FDA approved it for treatment of thyroid cancer with further approval for the same indication following in 2014 in the European Union and Japan. As is customary, it is still in multiple clinical trials in both combination and single-agent therapies. The second drug that probably came about from a *de novo* sourcing is ataluren (Translarna; **2**),[30] which was approved in the EU in 2014 and launched in Germany the same year for the treatment of patients with genetic disorders due to a "nonsense" mutation. The mechanism of this small molecule can be seen in a diagrammatic mode at the following URL: http://www.ptcbio.com/en/pipeline/ataluren-translarna/. However, the first anticancer drug constructed by use of fragment screening and model fitting, vemurafenib (**3**), was approved by the FDA in 2011, and the story behind this and other small-molecule antitumor agents was well described in a review in 2012 by Hoelder et al., which should be consulted for more information on this style of approach to drug discovery.[31]

As mentioned by the present 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. An expected surge in productivity, however, did not appear to materialize in the years from 2004 to 2014. Thus, the number of new active substances (NASs) from our data set, also known as new chemical entities (NCEs), which we consider to encompass all molecules, including biologics and vaccines, hit a 24-year low of 24 in 2004 (although 7, or 29%, of these were assigned to the "ND" category), leading to a rebound to 52 in 2005, with 25% being "N" or "ND" and 37% being biologics ("B") or vaccines ("V"). The next four years from 2006 to 2009 averaged 40, with 35−45% being vaccines or biologics, although in these four years, four "botanicals" were approved. In 2010 and 2011, the figures again dropped to 33 and 34, respectively, but then in 2012 to 2014, the figures rebounded to 60, 47, and 65, respectively, but biologics and vaccines were significant proportions of these totals.

These figures are further developed covering the full details by year in Figures 2 and 4 (see the Discussion section below), together with other graphs such as Figure 5, showing total small molecules/year, Figure 6, showing the percentage of natural-product-based compounds and their derivatives. Plus in this review, we have also added the S* series of compounds to these.

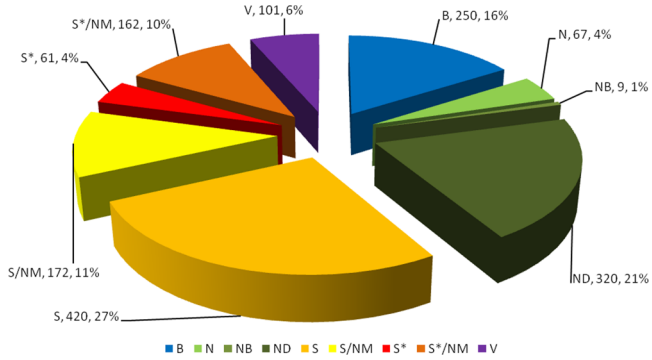


Figure 1. All new approved drugs 1981−2014; n = 1562.

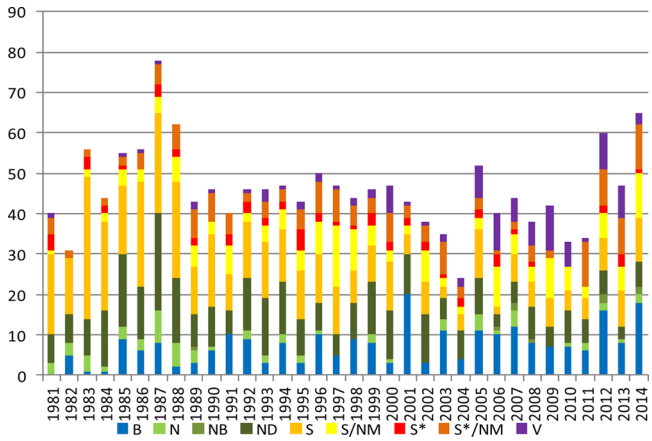


Figure 2. All new approved drugs by source/year.

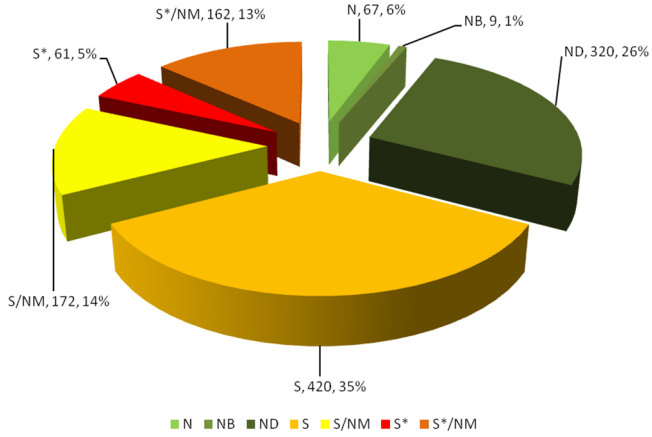


Figure 3. All small-molecule approved drugs 1981−2014s; n = 1211.

The use of the S* classification originally arose as a result of doubts expressed by some colleagues working in the chemical synthesis area who questioned the claim that nucleoside analogues synthesized in the laboratory actually evolved from the discoveries by the Bergmann group in the 1950s of the arabinose-containing natural products from marine sponges.[32−34]

The justification for the addition of the "S*" category to natural-product-based compounds and their derivatives in this review is that a large number of the "S*" structures are based on naturally derived nucleosides or very closely related scaffolds, and their relevance to drug discovery will be published in a review in the first half of 2016. Figure 7 then shows the percentage of just

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

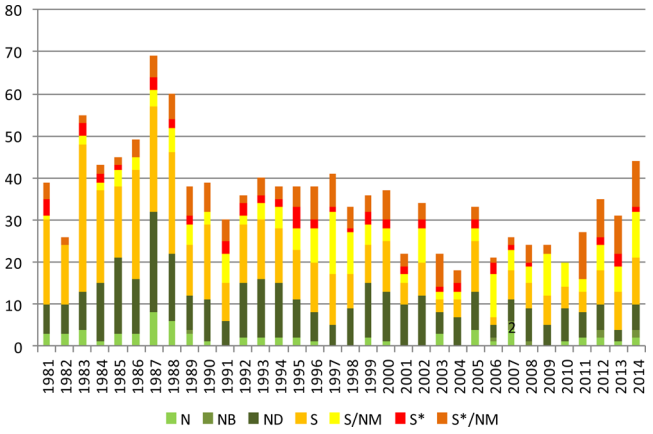


Figure 4. All small-molecule approved drugs by source/year.

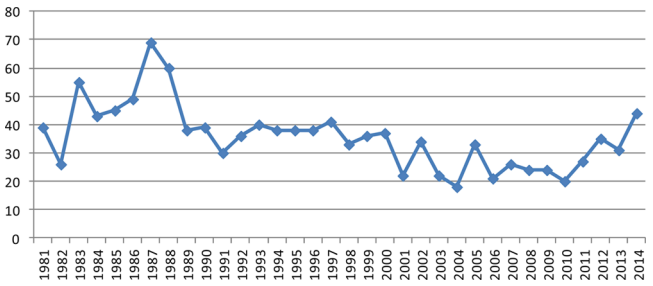


Figure 5. Total small molecules/year.

the "N*" categories over the 34 years. What is of significant importance in this area is the very recent paper from the Gerwick group demonstrating the isolation of spongosine (**4**) from a *Vibrio harveyi* strain isolated from the same sponge species (*Tectitethya crypta*) as used by Bergmann 60+ years earlier.[35] However, to allow for comparisons with earlier reviews, we have not altered the categories in the analyses. Fortunately, however, research is still being conducted by (bio)synthetic groups on the modification of active natural product skeletons as leads to novel agents. This was exemplified recently by publications in 2014–2015 from the groups of Szychowski et al.,[36] Bathula,[37] Thaker,[38] Williams,[39] Miller,[40] and Novaes et al.[41] and an excellent perspective by Nicolaou in 2014.[42]

Against this backdrop, we now present an updated analysis of the role of natural products in the drug discovery and development process, dating from January 1981 through December 2014. As in our earlier analyses,[1−4] we have consulted the *Annual Reports of Medicinal Chemistry*, in this case from 1984 to 2014,[43−74] and to obtain more comprehensive coverage of the 1981−2014 time frame we have added data from the publication *Drug News and Perspective*,[75−95] the successor listings in *Drugs of Today*,[96−101] and searches of the Prous (now Thomson-Reuter's *Integrity*) database, as well as by including information from individual investigators. As in the last review, the biologics data prior to 2005 were updated using information culled from disparate sources that culminated in a 2005 review on biopharmaceutical drugs.[102] We have continued our attempts to capture vaccine data for the past few years, but this area of the database is still not as complete as we would hope.

As in previous reviews in this series, we have continued to include relevant references in a condensed form in Tables 3−6 and 9−11. 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. We should point out that due to a change effective in 2015, the ARMC is now known as *Medicinal Chemistry Reviews*. Similarly, "DNP ##" refers to the volume of *Drug News and Perspective* and the corresponding page(s), although this journal has now ceased publication as of the 2010 volume. Similarly "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 (now Thomson-Reuters, *Integrity*) database. Finally, in the overall listing of antitumor agents from the middle 1930s to 2014 (Table 9) we have used "Boyd" to refer to a review article[103] on clinical antitumor agents, an earlier book on the same subject,[104] and "M'dale" to refer to *Martindale*[105] with the relevant page noted.

It must be noted that the "year" header in all tables is formally equivalent to the "year of introduction" of the drug in the first country in which it was approved. We only count a drug once,

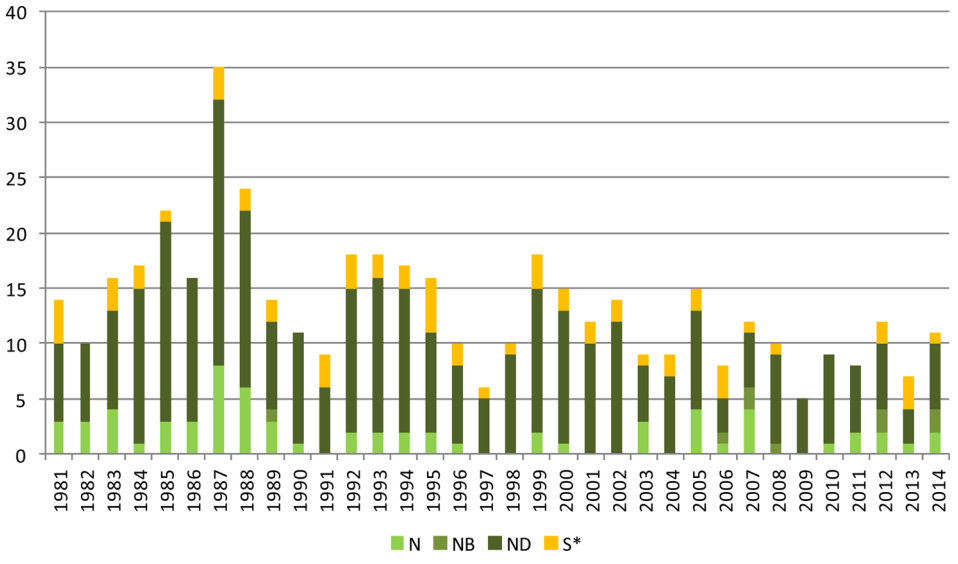


Figure 6. N, NB, ND, and S* categories by year, 1981−2014.

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

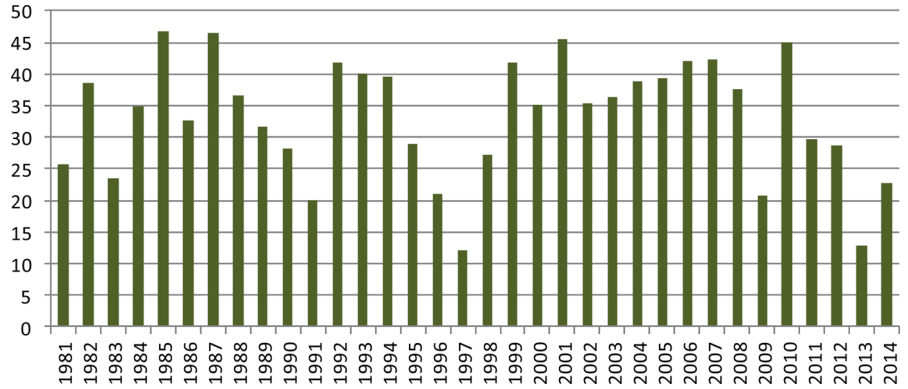


Figure 7. Percentage of N* by year, 1981−2014.

even if subsequently it is approved in other countries or for other indications. Over the years, we have realized 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. We have generally taken the earliest year in the absence of further information.

RESULTS

As in previous reviews, we have, except in a case that will be noted later in this review where a therapy used NCEs (two unapproved agents) in the approved combination, only covered NCEs in the present analysis. As mentioned in earlier reviews, if one reads the U.S. FDA and PhRMA Web sites, the numbers of New Drug Application (NDA) approvals are in the high tens in some of the past few years. The FDA Drugs Database needs to be assessed by anyone using it for drugs previously approved in other countries versus new drugs only approved in the USA to obtain more accurate figures, and there will be differences due to our noting drugs approved the first time anywhere and then not counting the same compound the first time it was approved by the FDA. Using our data (see Figures 2, 4, and 5) the number of NCEs has ranged from the 20's to just over 50 per year from 1989 to 2011 and in 2013 for approved NCEs (note that Figures 4 and 5 count only small molecules), although in 2012 and 2014 the figures reached 60 and 65, respectively. The reader needs to bear in mind that our vaccine numbers are not complete, so the overall numbers could increase. If one now removes biologicals and vaccines, thus noting only "small molecules" (including peptides such as Byetta), then the figures show that over the same time frame the numbers have ranged from close to 40 for most of the 1989 to 2000 time frame (except for 2002) to close to 20 from 2001 to 2010, with the exception of 2002 and 2004, when the figures climbed above 30. In the last four years (2011 to 2014), the numbers have now climbed from 28 in 2011 to 44 (cf., Figures 2 and 4).

Now with 34 years of data to analyze, it was decided to add another graph to the listings, together with one of significant interest to the natural products community. In Figure 6 we have plotted a bar graph from 1981 to 2014 showing the results in numbers/year when the designations used are an "N" or a subdivision ("NB" or "ND"). This time, we have deliberately included the "S*" designation (for the reasons elaborated earlier), which could be considered as "inspired by a natural product structure". This figure demonstrates that even in 2014 10 of the 44 approved small-molecule drugs are "N", "NB", and "ND" with one "S*", which account for 25% of the 44 approved NCEs that year. If we just use the "N", "NB", and "ND" designations over the complete 34 years, then the mean and standard deviation figures in percentages are 33 ± 9, and in Figure 7 we have shown the percentage for "N*" values by year. Readers can determine their own ratios for their "year of interest", as desired.

As in our earlier reviews,[1−4] 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, unmodifed in structure, though might be semi- or totally synthetic

"NB": Natural product "botanical drug" (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 extension of the "S" and "S*" categories from 2003 onward)

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 5 mM. We have continued to classify most PTK inhibitors that are approved as drugs under the "/NM" category for exactly the same reasons as elaborated in the 2003 review,[2] although nowadays, some later kinase inhibitors are not competitive inhibitors of ATP and thus would not be classified this way. The latest discussion on this aspect of PTKs can be read in the 2015 paper by Fabbro et al.[106] (Fabbro can be considered the "developmental father of Gleevec"), which should be read in conjunction with his 2002 paper on PTKs as targets.[107] In addition, the very interesting recent review by Vijayan et al.[108] should be consulted, as it demonstrates, together with the 2015 paper from Fabbro et

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 2. New Chemical Entities and Medical Indications by Source of Compound 1/1/1981−12/31/2014[a]

indication	total	B	N	NB	ND	S	S/NM	S*	S*/NM	V
COPD	8						3		5	
analgesic	17		1			11	3	2		
anesthetic	5					5				
anti-Alzheimer	6	1	1		1		3			
anti-Gaucher's disease	5	3			1				1	
anti-Parkinsonian	12				1	1	5	1	4	
antiallergic	18		1	1	4	12				
antianginal	5					5				
antiarrhythmic	17		1			14			2	
antiarthritic	22	6	1	1	3	4	6		1	
antiasthmatic	14	1			3	2	6		2	
antibacterial	140	1	11		71	29			1	27
anticancer	174	33	17	1	38	23	20	13	24	5
anticoagulant	22	5			13			1	3	
antidepressant	27					8	17		2	
antidiabetic, types 1 and 2	52	23	1		6	4	11	1	6	
antiemetic	11					1	2		8	
antiepileptic	17				2	11		2	2	
antifungal	32	1			3	25	3			
antiglaucoma	14				5		5	1	3	
antihistamine	14					14				
antihyperprolactinemia	4				4					
antihypertensive	80				2	28	15	2	33	
anti-inflammatory	51	1			13	37				
antimigraine	10					2	1		7	
antiobesity	6				1	1	4			
antiparasitic	16		2		5	5		3		1
antipsoriatic	11	4		1	3		1	1	1	
antipsychotic	11					3	6		2	
antithrombotic	30	13	1		5	2	6		3	
antiulcer	34	1	1		12	20				
antiviral	139	14			4	14	5	24	17	61
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	9				8		1			
cystic fibrosis	4	1				3				
diuretic	6					4	2			
erythropoiesis	5	5								
gastroprokinetic	4					1	2		1	
hematopoiesis	7	7								
hemophilia	19	19								
hemostatic	4	4								
hormone	22	12			10					
hormone replacement therapy	8				8					
hyperphosphatemia	5					5				
hypnotic	12					12				
hypocholesterolemic	13		4		1	2	1		5	
hypolipidemic	8		1			7				
immunomodulator	4	2	1		1					
immunostimulant	12	6	3		2	1				
immunosuppressant	14	6	5		3					
irritable bowel syndrome	5				1	1			3	
macular degeneration	6	4			1	1				
male sexual dysfunction	5								5	
multiple sclerosis	10	4			2	2		1	1	
muscle relaxant	10				4	2	1	3		
neuroleptic	9					1	6		2	

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 2. continued

indication	total	B	N	NB	ND	S	S/NM	S*	S*/NM	V
nootropic	8				3	5				
osteoporosis	6	3			2	1				
platelet aggregation inhibitor	4				3		1			
respiratory distress syndrome	7	4	1			1	1			
urinary incontinence	6					2	3		1	
vasodilation	5				3	2				
vulnerary	8	5			2	1				
grand total	1328	189	54	4	268	359	149	55	156	94

[a]Diseases where ≤3 drugs approved 1981−2014: 234 drugs fall into this category and are subdivided as follows: B, 81; N, 15; ND, 46; S, 47, S/NM. 15; S*, 4; S*/NM, 18. The diseases covered the following; 5α-reductase inhibitor, ADHD, CAPS, CHF, CNS stimulant, Castleman's disease, Crohn's disease, Cushing's syndrome, Fabry's disease, 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, abortifacient, acromelagy, alcohol deterrent, allergic rhinitis, anabolic metabolism, analeptic, anemia, antisickle cell anemia, antismoking, antiacne, antiatherosclerotic, anticonvulsant, antidiarrheal, antidote, antiemphysemic, antihyperuricemia, antihypotensive, antinarcolepsy, antinarcotic, antinauseant, antiperistaltic, antiprogestogenic, 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, cardioprotective, cardiovascular disease, cartilage disorders, cervical dystonia, choleretic, chronic idiopathic constipation, cognition enhancer, congestive heart failure, constipation, coronary artery disease, cystinosis, cytoprotective, diabetic foot ulcers, diabetic neuropathies, digoxin toxicity, dispareunia, dry eye syndrome, dyslipidemia, dysuria, endometriosis, enzyme, expectorant, eye disorders, fertility inducer, free-running circadian disorder, gastroprotectant, genital warts, hematological, hemorrhage, hepatoprotectant, hereditary angioedema, homocystinuria, hyperammonemia, hypercholesterolemia (and familial), hyperparathyroidism, hyperphenylalaninemia, hypertriglyceridemia, hyperuricemia, hypoammonuric, hypocalciuric, hypogonadism, hyponatremia, idiopathic pulmonary fibrosis, idiopathic thrombocytopenia, immediate allergy, infertility (female), inflammatory bowel disease, insecticide, insomnia, joint lubricant, lipodystrophy (and in HIV), lipoprotein disorders, lipoprotein lipase deficiency, lupus erythematosus, mucolytic, mucopolysaccharidosis, mucositis, myleodysplasia, narcolepsy, nasal decongestant, neuropathic pain, neuroprotective, neutropenia, ocular inflammation, opiate detoxification, opiod-induced constipation, osteoarthritis, overactive bladder, ovulation, pancreatic disorders, pancreatitis, pertussis, photosensitizer, phytotoxicity in adults, pituitary disorders, porphyria, premature birth, premature ejaculation, progestogen, psychostimulant, pulmonary arterial hypertension, purpura fulminans, rattlesnake antivenom, reproduction, restenosis, schizophrenia, sclerosant, secondary hyperthryoidism, sedative, short bowel syndrome, skin photodamage, smoking cessation, strabismus, subarachnoid hemorrhage, thrombocytopenia, treatment of GH deficiency, ulcerative colitis, urea cycle disorders, uremic pruritis, urolithiasis, vaccinia complications, varicella (chicken pox), vasoprotective, venous thromboembolism.

al.,[106] that kinase modulation occurs in a large number of other diseases, and not just in cancer.

Thus, PTK inhibitors have a wide range of possible targets and, in the cases of some specific approved antitumor-directed kinase inhibitors, have a very large number of "targets" in the human kinome. Thus, sunitinib (**5**) affects a very considerable number of different kinase "families", whereas lapatinib (**6**) is restricted to one class, and the as yet unapproved PTKi selumetinib (AZD6244; **7**) appears to be quite specific. These effects can be seen in the figures in the 2015 paper by Fabbro et al.[106] and are further elaborated on by Tilgada et al.,[109] demonstrating that the targets of PTKi's are not just in cancer and related diseases. 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 new peptidic drug entities, although formally synthetic in nature, are simply produced by chemical 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. We gave some examples of this type of interplay in our 2012 review, in which we mentioned the path to the "sartans".[4]

Derivation of Oral Renin Inhibitors. Expanding upon this aspect of chemistry and pharmacology, we now will show how the first orally active renin inhibitor was derived starting from pepstatin. In Scheme 1 we show an idealized representation of the angiotensin system pathway, showing the physiological route from renin (an aspartic proteinase) through to the angiotensin-converting enzyme (ACE), to yield the hexapeptide angiotensin II. It was knowledge that this enzyme is a zinc-containing carboxy-peptidase that enabled the Squibb group back in the 1970s to synthesize the pseudodipeptide captopril (**8**) as the first ACE inhibitor to be approved by the FDA.

However, the "prime target" in the system is inhibition of renin since that is the enzyme that starts the cascade, and, unlike ACE, it does not hydrolyze the "kinin" peptides (bradykinin, etc.). Renin was known to be an aspartic proteinase, and it could be inhibited by the bacterial peptide pepstatin (**9**). This compound contains the unusual amino acid statine, which contains as a dipeptide mimic a hydroxyethylene isostere, and it was the basis of a long-term project at Merck to synthesize renin inhibitors, and later HIV-protease inhibitors, based on this substituent mimicking the transition state of the aspartic proteinase/substrate pair.[110,111] Although none of their peptide structures provided a renin inhibitor that was approved as a drug, their work demonstrated the potential for such substitutions to be effective drug leads, albeit from Ciba-Geigy (now Novartis), en route to an orally active renin inhibitor. The first of what were known as type-I inhibitors[112] contained the dipeptide isostere (2*S*,4*S*,5*S*)-5-amino-4-hydroxy-2-isopropyl-6-cyclohexylhexanoic acid at the P1−P1′ position and also mimicked angiotensinogen from residue P3 to P1′ using the nomenclature from Schetchter and Berger.[113]

The story of the search for orally active renin inhibitors, although formally nonpeptidic but still containing the hydroxyethylene transition state dipeptide isostere, was given in detail by Novartis scientists in two papers, demonstrating that the search

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 3. Antibacterial Drugs from 1/1/1981 to 12/31/2014 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	volume	page	source
raxibacumab	ABthrax	2012	I 336061		B
carumonam	Amasulin	1988	ARMC 24	298	N
daptomycin	Cubicin	2003	ARMC 39	347	N
fidaxomicin	Dificid	2011	DT 48(1)	40	N
fosfomycin trometamol	Monuril	1988	I 112334		N
isepamicin	Isepacin	1988	ARMC 24	305	N
micronomicin sulfate	Sagamicin	1982	P091082		N
miokamycin	Miocamycin	1985	ARMC 21	329	N
mupirocin	Bactroban	1985	ARMC 21	330	N
netilimicin sulfate	Netromicine	1981	I 070366		N
RV-11	Zalig	1989	ARMC 25	318	N
teicoplanin	Targocid	1988	ARMC 24	311	N
apalcillin sodium	Lumota	1982	I 091130		ND
arbekacin	Habekacin	1990	ARMC 26	298	ND
aspoxicillin	Doyle	1987	ARMC 23	328	ND
astromycin sulfate	Fortimicin	1985	ARMC 21	324	ND
azithromycin	Sunamed	1988	ARMC 24	298	ND
aztreonam	Azactam	1984	ARMC 20	315	ND
biapenem	Omegacin	2002	ARMC 38	351	ND
cefbuperazone sodium	Tomiporan	1985	ARMC 21	325	ND
cefcapene pivoxil	Flomox	1997	ARMC 33	330	ND
cefdinir	Cefzon	1991	ARMC 27	323	ND
cefditoren pivoxil	Meiact	1994	ARMC 30	297	ND
cefepime	Maxipime	1993	ARMC 29	334	ND
cefetamet pivoxil HCl	Globocef	1992	ARMC 28	327	ND
cefixime	Cefspan	1987	ARMC 23	329	ND
cefmenoxime HCl	Tacef	1983	ARMC 19	316	ND
cefminox sodium	Meicelin	1987	ARMC 23	330	ND
cefodizime sodium	Neucef	1990	ARMC 26	300	ND
cefonicid sodium	Monocid	1984	ARMC 20	316	ND
cefoperazone sodium	Cefobis	1981	I 127130		ND
ceforanide	Precef	1984	ARMC 20	317	ND
cefoselis	Wincef	1998	ARMC 34	319	ND
cefotetan disodium	Yamatetan	1984	ARMC 20	317	ND
cefotiam HCl	Pansporin	1981	I 091106		ND
cefozopran HCl	Firstcin	1995	ARMC 31	339	ND
cefpimizole	Ajicef	1987	ARMC 23	330	ND
cefpiramide sodium	Sepatren	1985	ARMC 21	325	ND
cefpirome sulfate	Cefrom	1992	ARMC 28	328	ND
cefpodoxime proxetil	Banan	1989	ARMC 25	310	ND
cefprozil	Cefzil	1992	ARMC 28	328	ND
cefsoludin sodium	Takesulin	1981	I 091108		ND
ceftaroline fosamil acetate	Teflaro	2011	DT 48(1)	40	ND
ceftazidime	Fortam	1983	ARMC 19	316	ND
cefteram pivoxil	Tomiron	1987	ARMC 23	330	ND
Ceftibuten	Seftem	1992	ARMC 28	329	ND
ceftizoxime sodium	Epocelin	1982	I 070260		ND
ceftobiprole medocaril	Zeftera	2008	ARMC 44	589	ND
ceftriaxone sodium	Rocephin	1982	I 091136		ND
cefuroxime axetil	Zinnat	1987	ARMC 23	331	ND
cefuzonam sodium	Cosmosin	1987	ARMC 23	331	ND
cetolozane/tazobactam	Zerbaxa	2014	DT 51(1)	47	ND
clarithromycin	Klaricid	1990	ARMC 26	302	ND
dalbavancin	Dalavance	2014	DT 51(!)	47	ND
dalfopristin	Synercid	1999	ARMC 35	338	ND
dirithromycin	Nortron	1993	ARMC 29	336	ND
doripenem	Finibax	2005	DNP 19	42	ND
ertapenem sodium	Invanz	2002	ARMC 38	353	ND
erythromycin acistrate	Erasis	1988	ARMC 24	301	ND
flomoxef sodium	Flumarin	1988	ARMC 24	302	ND
flurithromycin ethylsuccinate	Ritro	1997	ARMC 33	333	ND

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 3. continued

generic name	trade name	year introduced	volume	page	source
fropenam	Farom	1997	ARMC 33	334	ND
imipenem/cilastatin	Zienam	1985	ARMC 21	328	ND
lenampicillin HCI	Varacillin	1987	ARMC 23	336	ND
loracarbef	Lorabid	1992	ARMC 28	333	ND
meropenem	Merrem	1994	ARMC 30	303	ND
moxalactam disodium	Shiomarin	1982	I 070301		ND
oritavancin	Orbactiv	2014	DT 51(1)	47	ND
panipenem/betamipron	Carbenin	1994	ARMC 30	305	ND
quinupristin	Synercid	1999	ARMC 35	338	ND
retapamulin	Altabax	2007	ARMC 43	486	ND
rifabutin	Mycobutin	1992	ARMC 28	335	ND
rifamixin	Normix	1987	ARMC 23	341	ND
rifapentine	Rifampin	1988	ARMC 24	310	ND
rifaximin	Rifacol	1985	ARMC 21	332	ND
rokitamycin	Ricamycin	1986	ARMC 22	325	ND
roxithromycin	Rulid	1987	ARMC 23	342	ND
sultamycillin tosylate	Unasyn	1987	ARMC 23	343	ND
tazobactam sodium	Tazocillin	1992	ARMC 28	336	ND
telavancin HCl	Vibativ	2009	DNP 23	15	ND
telithromycin	Ketek	2001	DNP 15	35	ND
temocillin disodium	Temopen	1984	ARMC 20	323	ND
tigecycline	Tygacil	2005	DNP 19	42	ND
balafloxacin	Q-Roxin	2002	ARMC 38	351	S
bedaquiline	Sirturo	2012	1 386239		S
besifloxacin	Besivance	2009	DNP 23	20	S
ciprofloxacin	Ciprobay	1986	ARMC 22	318	S
enoxacin	Flumark	1986	ARMC 22	320	S
finafloxacin hydrochloride	Xtoro	2014	DT 51(1)	48	S
fleroxacin	Quinodis	1992	ARMC 28	331	S
garenoxacin	Geninax	2007	ARMC 43	471	S
gatilfloxacin	Tequin	1999	ARMC 35	340	S
gemifloxacin mesilate	Factive	2003	ARMC 40	458	S
grepafloxacin	Vaxor	1997	DNP 11	23	S
levofloxacin	Floxacin	1993	ARMC 29	340	S
linezolid	Zyvox	2000	DNP 14	21	S
lomefloxacin	Uniquin	1989	ARMC 25	315	S
moxifloxacin HCl	Avelox	1999	ARMC 35	343	S
nadifloxacin	Acuatim	1993	ARMC 29	340	S
nemonoxacin	Taigexyn	2014	DT 51(1)	48	S
norfloxacin	Noroxin	1983	ARMC 19	322	S
ofloxacin	Tarivid	1985	ARMC 21	331	S
pazufloxacin	Pasil	2002	ARMC 38	364	S
pefloxacin mesylate	Perflacine	1985	ARMC 21	331	S
prulifloxacin	Sword	2002	ARMC 38	366	S
rufloxacin hydrochloride	Qari	1992	ARMC 28	335	S
sitafloxacin hydrate	Gracevit	2008	DNP 22	15	S
sparfloxacin	Spara	1993	ARMC 29	345	S
taurolidine	Taurolin	1988	I 107771		S
tedizolid phosphate sodium	Sivextro	2014	DT 51(1)	47	S
temafloxacin hydrochloride	Temac	1991	ARMC 27	334	S
tosufloxacin	Ozex	1990	ARMC 26	310	S
trovafloxacin mesylate	Trovan	1998	ARMC 34	332	S
brodimoprin	Hyprim	1993	ARMC 29	333	S*/NM
	Bexsero	2013	DT 50(1)	69	V
	Prevenar 13	2009	DNP 23	17	V
	Quattrovac	2012	I 770186		V
	Synflorix	2009	DNP 23	17	V
	Typbar	2013	DT 50(1)	68	V
ACWY meningoccal PS vaccine	Mencevax	1981	I 420128		V
BK-4SP	Tetrabik	2012	I 697562		V
botulism antitoxin	Bat	2013	DT 50(1)	77	V

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 3. continued

generic name	trade name	year introduced	volume	page	source
DTPw-HepB-Hib	Quinvaxem	2006	DNP 20	26	V
DTP vaccines	Daptacel	2002	I 319668		V
H. influenzae b vaccine	Hibtitek	1989	DNP 03	24	V
H. influenzae b vaccine	Prohibit	1989	DNP 03	24	V
hexavalent vaccine	Hexavac	2000	DNP 14	22	V
hexavalent vaccine	Infantrix HeXa	2000	DNP 14	22	V
Hib-MenCY-TT	Menhibrix	2012	I 421742		V
MCV-4	Menactra	2005	DNP 19	43	V
MenACWY-CRM	Menveo	2010	I 341212		V
MenACWY-TT	Nimenrix	2012	I 421745		V
meningitis b vaccine	MeNZB	2004	DNP 18	29	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
MnB rLP2086	Trumenba	2014	DT 51(1)	51	V
oral cholera vaccine	Orochol	1994	DNP 08	30	V
pneumococcal vaccine	Prevnar	2000	DNP 14	22	V
PsA-TT	MenAfriVac	2010	I 437718		V
Vi polysaccharide typhoid vaccine	Typherix	1998	DNP 12	35	V

involved significant computerized structure−activity relationships using the crystal structure of human renin to optimize the chemistry, before finally leading to the drug candidate, SPP-100, which became the drug aliskiren (**10**) and gained FDA approval in March 2007 and EMA approval in August 2007. The first paper, in 2000,[114] gave the chemical basis for the initial discoveries of pseudopeptidic agents and the use of structure-based drug design with modifications around the initial type-I inhibitor (CGP 38′560; **11**). The second paper, published in 2003,[115] gave the next chapter in the story, the work leading up to aliskiren. Finally, a thorough analysis of the various molecules and routes leading to aliskiren was published by Novartis scientists in 2010, and this should be consulted for the full story.[116]

Also of interest are some recent publications that under certain conditions could almost be considered as potential for "repurposing" of this drug and perhaps others with the same target. Following a study on the conformation of aliskiren in solution and when bound to its receptor, by Politi et al., in 2011[117] the data were used to calculate binding of aliskiren to a model of the HIV protease (an aspartic proteinase). This study also demonstrated that the FDA-approved (2013) SGLT-2 inhibitor canagliflozin (**12**) and the approved HIV protease inhibitor darunavir (**13**) may have cross-activities in renin inhibition as well as their regular approved pharmacological targets, thus potentially repurposing these compounds.[118]

Biologically Active Peptides. 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.[119]

Modifications of Natural Products by Combinatorial Methods. These techniques often produce entirely different compounds that may bear little if any resemblance to the original lead, but are legitimately assignable to the "/NM" category. In addition to the citations given in our previous reviews covering these methodologies, there have been some recent publications that can be consulted in order to demonstrate how "privileged structures from Nature" are demonstrated sources of molecular skeletons around which one may build libraries.[120−123]

Overview of Results. The data that have been analyzed in a variety of ways are presented as a series of bar graphs and pie charts and two major tables in order to establish the overall picture and then are further subdivided into some major therapeutic areas using a tabular format. The time frame covered is the 34 years from January 1, 1981, to December 31, 2014.

- New Approved Drugs: From all source categories; pie chart (Figure 1)
- New Approved Drugs: By source/year; bar graph (Figure 2)
- Sources of All NCEs: Where four or more drugs were approved per medical indication, their sources are shown, and listings of diseases with ≤3 approved drugs (Table 2)
- Sources of Small-Molecule NCEs: All subdivisions; pie chart (Figure 3)
- Sources of Small-Molecule NCEs: By source/year; bar graph (Figure 4)
- Total Small Molecules: By year; point chart (Figure 5)
- N/NB/ND and S* Categories: By year; bar graph (Figure 6)
- Percentage of N* Sources: By year; bar graph (Figure 7)
- Antibacterial Drugs: Generic and trade names, year, reference, and source (Table 3)
- Antifungal Drugs: Generic and trade names, year, reference, and source (Table 4)
- Antiviral Drugs: Generic and trade names, year, reference, and source (Table 5)
- Antiparasitic Drugs: Generic and trade names, year, reference, and source (Table 6)
- Anti-infective Drugs: All molecules, source, and numbers (Table 7)
- Anti-infective Drugs: Small molecules, source, and numbers (Table 8)
- Anticancer Drugs: Generic and trade names, year, reference by source (Table 9; Figure 8 all drugs pie chart; Figure 9, small molecules pie chart)
- All Anticancer Drugs (very late 1930s−12/2014): Generic and trade names, year, and reference by source (Table 10; Figure 10 pie chart; Figure 11, bar graph)

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 4. Antifungal Drugs from 1/1/1981 to 12/31/2010 Organized Alphabetically by Generic Name within Source

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

- Antidiabetic Drugs: Generic and trade names, year, reference, and source (Table 11)

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

Inspection of the rate of NCE approvals as shown in Figures 2 and 4−7 demonstrate that even in 2014 the natural products field is still producing, or is involved in, ∼40% of all small molecules in the years 2000−2008, with a drop to ∼20% in 2009, followed by a rebound to 45% in 2010, and then fluctuation between a low of ∼13% in 2013 to between 25% and 30% in the other years of the second decade of the 21st century. The mean and standard deviation for these 15 years are 34 ± 9%, without including any of the natural-product-inspired classifications ("S*", "S*/NM", and "S/NM").

As was shown in the 2012 review, a significant number of all NCEs still fall into the categories of biological ("B") or vaccines ("V"), with 351 of 1562, or 23% (differs slightly from Figure 1 due to rounding), over the full 34-year period, and it is admitted that not all of the vaccines approved in these 34 years have been identified. We hope that in the last 14 or 15 years a majority have been captured, although some of the more obscure anti-influenza variants may not have been. Thus, the proportion of approved vaccines may well be higher over the longer time frame. Inspection of Figure 2 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. If the three "N" categories are included, then the proportions of formally nonsynthetics are even higher for these years, although this figure would increase if the "S*" variants are included.

***De Novo* Combinatorial Drugs.** As mentioned earlier, in spite of many years of work by the pharmaceutical industry devoted to high-throughput screening of very significant numbers of combinatorial chemistry products (cf. Macarron's[20,24,25] and Wassermann's[26] papers on the industrial perspectives), during this time period, only two approved drugs could be found that fall under the *de novo* combinatorial category, sorafenib (**1**) and ataluren (**2**), with vemurafenib (**3**) potentially falling into this category due to the use of fragment-based methods.

Natural Product Mimics. Overall, of the 1562 NCEs covering all diseases/countries/sources in the years 01/1981−12/2014, and using the "NM" classifications introduced in our 2003 review,[2] the 334 compounds falling into these categories accounted for 21%, or if using just the small molecules where the divisor drops to 1211, the figure becomes 28%. This demonstrates the influence of "other than formal synthetics" on drug discovery and approval (Figures 1 and 3). In the 2012 review, the corresponding figures were ∼20% for all drugs and 25% for small molecules.[4]

Disease Area Breakdowns. It should be noted before proceeding with this and subsequent sections that we altered some of the "disease nomenclature terminology", for example, rolling in all antidiabetic treatments under one category rather than subdividing into types 1 and 2. Thus, a direct comparison of Table 2 in this review with its predecessor tables needs to take such modifications into account. Inspection of Table 2 demonstrates that, overall, the major disease areas that have been investigated (in terms of numbers of drugs approved) in the pharmaceutical industry continue to be infectious diseases (microbial, parasitic, and viral), cancer, hypertension, antidiabetic, and inflammation, all with over 50 approved drug

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 5. Antiviral Drugs from 1/1/1981 to 12/31/2014 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	volume	page	source
	Oralgen	2007	I 415378		B
IGIV-HB	Niuliva	2009	DNP 23	16	B
immunoglobulin intravenous	Gammagard Liquid	2005	I 231564		B
interferon alfa	Alfaferone	1987	I 215443		B
interferon alfa-2b	Viraferon	1985	I 165805		B
interferon alfacon-1	Infergen	1997	ARMC 33	336	B
interferon alfa-n1	Wellferon	1986	I 125561		B
interferon alfa-n3	Alferon N	1990	DNP 04	104	B
interferon beta	Frone	1985	I115091		B
palivizumab	Synagis	1998	DNP 12	33	B
peginterferon alfa-2a	Pegasys	2001	DNP 15	34	B
peginterferon alfa-2b	Pegintron	2000	DNP 14	18	B
resp syncytial virus IG	RespiGam	1996	DNP 10	11	B
thymalfasin	Zadaxin	1996	DNP 10	11	B
enfuvirtide	Fuzeon	2003	ARMC 39	350	ND
laninamivir octanoate	Inavir	2010	I 340894		ND
oseltamivir	Tamiflu	1999	ARMC 35	346	ND
zanamivir	Relenza	1999	ARMC 35	352	ND
daclatasvir dihydrochloride	Daklinza	2014	DT 51(1)	48	S
dasabuvir	Exviera	2014	DT 51(1)	50	S
delavirdine mesylate	Rescriptor	1997	ARMC 33	331	S
dolutegravir	Tivicay	2013	DT 50(1)	63	S
efavirenz	Sustiva	1998	ARMC 34	321	S
elvitegravir	Viteka	2013	DT 50(1)	63	S
foscarnet sodium	Foscavir	1989	ARMC 25	313	S
imiquimod	Aldara	1997	ARMC 33	335	S
maraviroc	Celsentri	2007	ARMC 43	478	S
nevirapine	Viramune	1996	ARMC 32	313	S
propagermanium	Serosion	1994	ARMC 30	308	S
raltegravir potassium	Isentress	2007	ARMC 43	484	S
rilpivirine hydrochloride	Edurant	2011	DT 48(1)	41	S
rimantadine HCI	Roflual	1987	ARMC 23	342	S
asunaprevir	Sunvepra	2014	DT 51(1)	48	S/NM
cobicistat	Tybost	2013	DT 50(1)	63	S/NM
darunavir	Prezista	2006	DNP 20	25	S/NM
ledipasvir	Harvoni	2014	DT 51(1)	48	S/NM
peramivir	PeramiFlu	2010	I 273549		S/NM
abacavir sulfate	Ziagen	1999	ARMC 35	333	S*
acyclovir	Zovirax	1981	I 091119		S*
adefovir dipivoxil	Hepsera	2002	ARMC 38	348	S*
cidofovir	Vistide	1996	ARMC 32	306	S*
clevudine	Levovir	2007	ARMC 43	466	S*
didanosine	Videx	1991	ARMC 27	326	S*
emtricitabine	Emtriva	2003	ARMC 39	350	S*
entecavir	Baraclude	2005	DNP 19	39	S*
epervudine	Hevizos	1988	I 157373		S*
etravirine	Intelence	2008	DNP 22	15	S*
famciclovir	Famvir	1994	ARMC 30	300	S*
ganciclovir	Cymevene	1988	ARMC 24	303	S*
inosine pranobex	Imunovir	1981	I 277341		S*
lamivudine	Epivir	1995	ARMC 31	345	S*
penciclovir	Vectavir	1996	ARMC 32	314	S*
sofosbuvir	Solvadi	2013	DT 50(1)	64	S*
sorivudine	Usevir	1993	ARMC 29	345	S*
stavudine	Zerit	1994	ARMC 30	311	S*
telbividine	Sebivo	2006	DNP 20	22	S*
tenofovir disoproxil fumarate	Viread	2001	DNP 15	37	S*
valaciclovir HCl	Valtrex	1995	ARMC 31	352	S*
valganciclovir	Valcyte	2001	DNP 15	36	S*
zalcitabine	Hivid	1992	ARMC 28	338	S*
zidovudine	Retrovir	1987	ARMC 23	345	S*

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 5. continued

generic name	trade name	year introduced	volume	page	source
amprenavir	Agenerase	1999	ARMC 35	334	S*/NM
atazanavir	Reyataz	2003	ARMC 39	342	S*/NM
boceprevir	Victrelis	2011	DT 48(1)	41	S*/NM
favipiravir	Avigan	2014	DT 51(1)	50	S*/NM
fomivirsen sodium	Vitravene	1998	ARMC 34	323	S*/NM
fosamprenevir	Lexiva	2003	ARMC 39	353	S*/NM
indinavir sulfate	Crixivan	1996	ARMC 32	310	S*/NM
lopinavir	Kaletra	2000	ARMC 36	310	S*/NM
neflinavir mesylate	Viracept	1997	ARMC 33	340	S*/NM
ombitasvir	Viekira Pak	2014	DT 51(1)	50	S*/NM
paritaprevir	Viekira Pak	2014	DT 51(1)	50	S*/NM
ritonavir	Norvir	1996	ARMC 32	317	S*/NM
saquinavir mesylate	Invirase	1995	ARMC 31	349	S*/NM
simeprevir	Sovirad	2013	DT 50(1)	63	S*/NM
telaprevir	Incivek	2011	DT 48(1)	41	S*/NM
tipranavir	Aptivus	2005	DNP 19	42	S*/NM
vaniprevir	Vanihep	2014	DT 51(1)	49	S*/NM
	ACAM-2000	2007	I 328985		V
	Bilive	2005	DNP 19	43	V
	Celtura	2009	DNP 23	17	V
	Celvapan	2009	DNP 23	17	V
	Daronix	2007	I 427024		V
	Fluval P	2009	DNP 23	17	V
	Fluzone Quadrivalent	2013	DT 50(1)	68	V
	Focetria	2009	DNP 23	17	V
	Grippol Neo	2009	DNP 23	16	V
	Hexyon	2013	DT 50(1)	69	V
	Imvanex	2013	DT 50(1)	69	V
	Optaflu	2007	I 410266		V
	Pandremix	2009	DNP 23	17	V
	Panenza	2009	DNP 23	17	V
	Panflu	2008	DNP 22	16	V
	Vaxiflu-S	2010	I 698015		V
	VariZIG	2005	I 230590		V
	Vepacel	2012	I 768351		V
9vHPV	Gardasil 9	2014	DT 51(1)	52	V
HPV vaccine	Gardasil	2006	DNP 20	26	V
anti-Hep B immunoglobulin	HepaGam B	2006	DNP 20	27	V
antirabies vaccine	Rabirix	2006	DNP 20	27	V
attenuated chicken pox vaccine	Merieux Varicella	1993	DNP 07	31	V
BBIL/JEV	Jenvac	2013	DT 50(1)	68	V
chimerivax-JE	Imojev	2012	I 292954		V
CSL-401	Panvax	2008	DNP 22	16	V
FLU-Q-QIV	Fluarix Quadrivalent	2012	DT 50(1)	68	V
GSK-1562902A	Prepandrix	2008	DNP 22	16	V
GSK-2282512A	Fluarix Quadrivalent	2012	I 709665		V
H5N1 avian flu vaccine		2007	I 440743		V
hepatitis a vaccine	Aimmugen	1995	DNP 09	23	V
hepatitis a vaccine	Havrix	1992	DNP 06	99	V
hepatitis a vaccine	Vaqta	1996	DNP 10	11	V
hepatitis b vaccine	Biken-HB	1993	DNP 07	31	V
hepatitis b vaccine	Bio-Hep B	2000	DNP 14	22	V
hepatitis b vaccine	Engerix B	1987	I 137797		V
hepatitis b vaccine	Fendrix	2005	DNP 19	43	V
hepatitis b vaccine	Hepacure	2000	DNP 14	22	V
hepatitis b vaccine	Meinyu	1997	DNP 11	24	V
hepatitis a and b vaccine	Ambirix	2003	I 334416		V
HN-VAC	HNVAC	2010	I 684608		V
inact hepatitis a vaccine	Avaxim	1996	DNP 10	12	V
influ A (H1N1) monovalent		2010	I 678265		V
influenza vaccine	Invivac	2004	I 391186		V

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 5. continued

generic name	trade name	year introduced	volume	page	source
influenza vaccine	Optaflu	2008	DNP 22	16	V
influenza virus (live)	FluMist	2003	ARMC 39	353	V
influenza virus vaccine	Afluria	2007	I 449226		V
KD-295		2014	DT 51(1)	52	V
measles/rubella vaccine		2011	DT 48(1)	44	V
Medi-3250	FluMist Quadrivalent	2012	I 669909		V
MR vaccine	Mearubik	2005	DNP 19	44	V
rec hepatitis B vaccine	Supervax	2006	DNP 20	27	V
rotavirus vaccine	Rotarix	2005	DNP 18	29	V
rotavirus vaccine	Rota-Shield	1998	DNP 12	35	V
rotavirus vaccine	Rotateq	2006	DNP 20	26	V
rubella vaccine	Ervevax	1985	I 115078		V
varicella virus vaccine	Varivax	1995	DNP 09	25	V
VCIV	PreFluCel	2010	I 444826		V
zoster vaccine live	Zostavax	2006	DNP 20	26	V

Table 6. Antiparasitic Drugs from 1/1/1981 to 12/31/2014 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	volume	page	source
artemisinin	Artemisin	1987	ARMC 23	327	N
ivermectin	Mectizan	1987	ARMC 23	336	N
arteether	Artemotil	2000	DNP 14	22	ND
artemether	Artemetheri	1987	I 90712		ND
artesunate	Arinate	1987	I 91299		ND
eflornithine HCl	Ornidyl	1990	DNP 04	104	ND
mefloquine HCI	Fansimef	1985	ARMC 21	329	ND
albendazole	Eskazole	1982	I 129625		S
delamanid	Deltyba	2014	DF 51(1)	48	S
halofantrine	Halfan	1988	ARMC 24	304	S
lumefantrine	?	1987	I 269095		S
quinfamide	Amenox	1984	ARMC 20	322	S
atovaquone	Mepron	1992	ARMC 28	326	S*
bulaquine/ chloroquine	Aablaquin	2000	DNP 14	22	S*
trichomonas vaccine	Gynatren	1986	I 125543		V

therapies. It should be noted, however, that the numbers of approved drugs/disease do not correlate with the "value" as measured by sales. For example, the best-selling drug of all at the moment is atorvastatin (Lipitor), a hypocholesterolemic descended directly from a microbial natural product, which sold over (U.S.) $11 billion in 2004, and, if one includes sales by Pfizer and Astellas Pharma over the 2004 to 2014 time frames, sales have hovered in the range (U.S.) $12−14 billion depending upon the year. However, this figure is almost sure to be eclipsed in short order by the new drugs approved for hepatitis C treatments such as sofosbuvir (**14**), which is a masked nucleotide, but is currently classified by us as an "S*", although it is obviously based upon an NP scaffold.

Table 8. Small-Molecule Anti-infective (Antibacterial, Fungal, Parasitic, and Viral) Drugs (n = 221)

indication	total	N	ND	S	S/NM	S*	S*/NM
antibacterial	112	11	71	29			1
antifungal	31		3	25	3		
antiparasitic	14	2	5	5		2	
antiviral	64		4	14	5	24	17
total	221	13	83	73	8	26	18
percentage	100	5.9	37.6	33.0	3.6	11.8	8.1

Anti-infectives in General. This is the major category by far including antiviral vaccines, with 326 (25%) of the total drug entities (1328 for indications ≥4; Table 2) falling into this one major human disease area. On further analysis (Tables 7 and 8), the influence of biologicals and vaccines in this disease complex is such that only 22% are synthetic in origin (Table 7). If one considers only small molecules (reducing the total by 105 to 221; Table 8), then the synthetic figure goes up to 33%, marginally greater than in our 2012 report.[4] As reported previously,[1−4] these synthetic drugs tend to be of two basic chemotypes, the azole-based antifungals and the quinolone-based antibacterials.

Anitbacterial Agents. Nine small-molecule drugs were approved in the antibacterial area from January 2011 to December 2014. One, fidaxomycin (**15**), was classified as an "N"; four were classified as "ND", with the first, ceftaroline (**16**), being a semisynthetic cephalosporin, the second being another cephalosporin derivative, cetolozane (**17a**) in combination with

Table 7. All Anti-infective (Antibacterial, Fungal, Parasitic, and Viral) Drugs (n = 326)

indication	total	B	N	ND	S	S/NM	S*	S*/NM	V
antibacterial	141	1	11	71	29			1	28
antifungal	32	1		3	25	3			
antiparasitic	15		2	5	5		2		1
antiviral	138	14		4	14	5	24	17	60
total	326	16	13	83	73	8	26	18	89
percentage	100	4.9	4.0	25.5	22.4	2.4	8.0	5.5	27.3

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 9. Anticancer Drugs from 1/1/1981 to 12/31/2014 Organized Alphabetically by Generic Name within Source

generic name	trade name	year introduced	volume	page	source
	Rexin-G	2007	I 346431		B
131I-chTNT		2007	I 393351		B
alemtuzumab	Campath	2001	DNP 15	38	B
bevacizumab	Avastin	2004	ARMC 40	450	B
blinatumomab	Blincyto	2014	DT 51(1)	55	B
catumaxomab	Removab	2009	DNP 23	18	B
celmoleukin	Celeuk	1992	DNP 06	102	B
cetuximab	Erbitux	2003	ARMC 39	346	B
denileukin diftitox	Ontak	1999	ARMC 35	338	B
H-101		2005	DNP 19	46	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
nimotuzumab	BIOMAb EFGR	2006	DNP 20	29	B
nivolumab	Optivo	2014	DT 51(1)	56	B
obinutuzumab	Gazyva	2013	DT 50(1)	70	B
ofatumumab	Arzerra	2009	DNP 23	18	B
panitumumab	Vectibix	2006	DNP 20	28	B
pegaspargase	Oncaspar	1994	ARMC 30	306	B
pembrolizumab	Keytruda	2014	DT 51(1)	56	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
sipuleucel-T	Provenge	2010	I 259673		B
tasonermin	Beromun	1999	ARMC 35	349	B
teceleukin	Imumace	1992	DNP 06	102	B
tositumomab	Bexxar	2003	ARMC 39	364	B
trastuzumab	Herceptin	1998	DNP 12	35	B
aclarubicin	Aclacin	1981	P090013		N
aminolevulinic acid HCl	Levulan	2000	DNP 14	20	N
angiotensin II	Delivert	1994	ARMC 30	296	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
paclitaxel	Taxol	1993	ARMC 29	342	N
paclitaxel nanoparticles	Abraxane	2005	DNP 19	45	N
paclitaxel nanoparticles	Nanoxel	2007	I 422122		N
paclitaxel nanoparticles	Genexol-PM	2007	I 811264		N
paclitaxel nanoparticles	PICN	2014	DT 51(1)	58	N
pentostatin	Nipent	1992	ARMC 28	334	N
peplomycin	Pepleo	1981	I090889		N
romidepsin	Istodax	2010	DNP 23	18	N
trabectedin	Yondelis	2007	ARMC 43	492	N
solamargines	Curaderm	1989	DNP 03	25	NB
abiratenone acetate	Zytiga	2011	DT 48(1)	44	ND
alitretinoin	Panretin	1999	ARMC 35	333	ND
aminolevulinic-CO_2CH_3	Metvix	2001	DNP 15	34	ND
amrubicin HCl	Calsed	2002	ARMC 38	349	ND
belotecan hydrochloride	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

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 9. continued

generic name	trade name	year introduced	volume	page	source
docetaxel	Taxotere	1995	ARMC 31	341	ND
elliptinium acetate	Celiptium	1983	I091123		ND
epirubicin HCl	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
fulvestrant	Faslodex	2002	ARMC 38	357	ND
gemtuzumab ozogamicin	Mylotarg	2000	DNP 14	23	ND
hexyl aminolevulinate	Hexvix	2004	I 300211		ND
idarubicin hydrochloride	Zavedos	1990	ARMC 26	303	ND
irinotecan hydrochloride	Campto	1994	ARMC 30	301	ND
ixabepilone	Ixempra	2007	ARMC 43	473	ND
mifamurtide	Junovan	2010	DNP 23	18	ND
miltefosine	Miltex	1993	ARMC 29	340	ND
pirarubicin	Pinorubicin	1988	ARMC 24	309	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 hydrochloride	Zantrene	1990	ARMC 26	300	S
carboplatin	Paraplatin	1986	ARMC 22	318	S
flutamide	Drogenil	1983	ARMC 19	318	S
fotemustine	Muphoran	1989	ARMC 25	313	S
heptaplatin/SK-2053R	Sunpla	1999	ARMC 35	348	S
lobaplatin	Lobaplatin	1998	DNP 12	35	S
lonidamine	Doridamina	1987	ARMC 23	337	S
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 hydrochloride	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
sobuzoxane	Parazolin	1994	ARMC 30	310	S
sorafenib	Nexavar	2005	DNP 19	45	S
vismodegib	Erivedge	2012	I 473491		S
zoledronic acid	Zometa	2000	DNP 14	24	S
alectinib hydrochloride	Alecensa	2014	DT 51(1)	56	S/NM
anastrozole	Arimidex	1995	ARMC 31	338	S/NM
apatinib mesylate	Aitan	2014	DT 51(1)	56	S/NM
bicalutamide	Casodex	1995	ARMC 31	338	S/NM
bortezomib	Velcade	2003	ARMC 39	345	S/NM
camostat mesylate	Foipan	1985	ARMC 21	325	S/NM
ceritinib	Zykadia	2014	DT 51(1)	55	S/NM
dasatinib	Sprycel	2006	DNP 20	27	S/NM
enzalutamide	Xtandi	2012	I 438422		S/NM
erlotinib hydrochloride	Tarceva	2004	ARMC 40	454	S/NM
fadrozole HCl	Afema	1995	ARMC 31	342	S/NM

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 9. continued

generic name	trade name	year introduced	volume	page	source
gefitinib	Iressa	2002	ARMC 38	358	S/NM
imatinib mesilate	Gleevec	2001	DNP 15	38	S/NM
lapatinib ditosylate	Tykerb	2007	ARMC 43	475	S/NM
letrazole	Femara	1996	ARMC 32	311	S/NM
nilotinib hydrochloride	Tasigna	2007	ARMC 43	480	S/NM
pazopanib	Votrient	2009	DNP 23	18	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*
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 hydrochloride	Lonsurf	2014	DT 51(1)	58	S*
abarelix	Plenaxis	2004	ARMC 40	446	S*/NM
afatinib	Gilotrif	2013	DT 50(1)	69	S*/NM
axitinib	Inlyta	2012	I 38296		S*/NM
belinostat	Beleodaq	2014	DT 51(1)	56	S*/NM
bexarotene	Targretine	2000	DNP 14	23	S*/NM
bosutinib	Bosulif	2012	I 301996		S*/NM
cabozantinib S-malate	Cometriq	2012	I 379934		S*/NM
crizotinib	Xalkori	2011	DT 48(1)	45	S*/NM
dabrafenib mesilate	Tafinlar	2013	DT 50(1)	69	S*/NM
degarelix	Firmagon	2009	DNP 22	16	S*/NM
ibrutinib	Imbruvica	2013	DT 50(1)	71	S*/NM
idelalisib	Zydelig	2014	DT 51(1)	54	S*/NM
pemetrexed disodium	Alimta	2004	ARMC 40	463	S*/NM
ponatinib	Iclusig	2013	DT 50(1)	70	S*/NM
radotinib	Supect	2012	I 395674		S*/NM
raltiterxed	Tomudex	1996	ARMC 32	315	S*/NM
regorafenib	Stivarga	2012	I 395674		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
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
autologous tumor cell-BCG	OncoVAX	2008	DNP 22	17	V
bcg live	TheraCys	1990	DNP 04	104	V
melanoma theraccine	Melacine	2001	DNP 15	38	V
vitespen	Oncophage	2008	DNP 22	17	V

the well-known β-lactamase inhibitor tazobactam (**17b**); the third was the modified glycopeptide dalvabancin (**18**); and the fourth was another of this class, oritavancin (**19**). The two synthetic molecules included the first novel anti-TB scaffold for many years, bedaquiline (**20**), and another "floxacin", finafloxacin (**21**). Overall, in the antibacterial area, as shown in Table 7, small molecules account for 112 agents, with "N" and "ND" compounds accounting for just over 73% of the approved agents.

What should make biomedical scientists and physicians involved in antibacterial research in academia or industry very nervous is the recent report from Liu et al.,[124] in the journal *Lancet Infectious Disease* in the middle of November 2015, where they reported that the class of compounds used effectively as the last resort (the peptidic colistins) now have a resistance determinant known as mcr-1 appearing in microbes in treated patients and animals.

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 10. All Anticancer Drugs (Late 1930s to 12/31/2014) Organized Alphabetically by Generic Name within Source

generic name	year introduced	reference	page	source
131I-chTNT	2007	I 393351		B
alemtuzumab	2001	DNP 15	38	B
aldesleukin	1992	ARMC 25	314	B
bevacizumab	2004	ARMC 40	450	B
catumaxomab	2009	DNP 23	18	B
celmoleukin	1992	DNP 06	102	B
cetuximab	2003	ARMC 39	346	B
denileukin diftitox	1999	ARMC 35	338	B
H-101	2005	DNP 19	46	B
ibritumomab	2002	ARMC 38	359	B
interferon alfa2a	1986	I 204503		B
interferon, gamma-1a	1992	ARMC 28	332	B
interleukin-2	1989	ARMC 25	314	B
ipilimumab	2011	DT 48(1)	45	B
mobenakin	1999	ARMC 35	345	B
mogamulizumab	2012	I 433141		B
nimotuzumab	2006	DNP 20	29	B
nivolumab	2014	DT 51(1)	56	B
obinutuzumab	2013	DT 50(1)	70	B
ofatumumab	2009	DNP 23	18	B
panitumumab	2006	DNP 20	28	B
pegaspargase	1994	ARMC 30	306	B
pembrolizumab	2014	DT 51(1)	56	B
pertuzumab	2012	I 300439		B
racotumomab	2013	DT 50(1)	72	B
ramucirumab	2014	DT 51(1)	55	B
Rexin-G (trade name)	2007	I 346431		B
rituximab	1997	DNP 11	25	B
sipuleucel-T	2010	I 259673		B
tasonermin	1999	ARMC 35	349	B
teceleukin	1992	DNP 06	102	B
tositumomab	2003	ARMC 39	364	B
trastuzumab	1998	DNP 12	35	B
PICN (Trade Name)	2014	DT 51(1)	58	N
aclarubicin	1981	I 090013		N
actinomycin D	1964	FDA		N
angiotensin II	1994	ARMC 30	296	N
arglabin	1999	ARMC 35	335	N
asparaginase	1969	FDA		N
bleomycin	1966	FDA		N
carzinophilin	1954	Japan Antibiotics		N
chromomycin A3	1961	Japan Antibiotics		N
daunomycin	1967	FDA		N
doxorubicin	1966	FDA		N
homoharringtonine	2012	I 090682		N
ingenol mebutate	2012	I 328987		N
leucovorin	1950	FDA		N
masoprocol	1992	ARMC 28	333	N
mithramycin	1961	FDA		N
mitomycin C	1956	FDA		N
neocarzinostatin	1976	Japan Antibiotics		N
paclitaxel	1993	ARMC 29	342	N
paclitaxel nanopart (Abraxane)	2005	DNP 19	45	N
paclitaxel nanopart (Nanoxel)	2007	I 422122		N
paclitaxel nanopart (Genexol-PM)	2007	I 811264		N
pentostatin	1992	ARMC 28	334	N
peplomycin	1981	I 090889		N
romidepsin	2010	DNP 23	18	N
sarkomycin	1954	FDA		N
streptozocin	pre-1977	Carter		N
testosterone	pre-1970	Cole		N

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 10. continued

generic name	year introduced	reference	page	source
trabectedin	2007	ARMC 43	492	N
vinblastine	1965	FDA		N
vincristine	1963	FDA		N
solamargines	1989	DNP 03	25	NB
abiratenone acetate	2011	DT 48(1)	44	ND
alitretinoin	1999	ARMC 35	333	ND
aminolevulinic-CO_2CH_3	2001	DNP 15	34	ND
amrubicin HCl	2002	ARMC 38	349	ND
belotecan hydrochloride	2004	ARMC 40	449	ND
bf-200 ala	2012	I 431098		ND
brentuximab vedotin	2011	DT 48(1)	45	ND
cabazitaxel	2010	I 287186		ND
calusterone	1973	FDA		ND
carfilzomib	2012	I 413092		ND
cladribine	1993	ARMC 29	335	ND
cytarabine ocfosfate	1993	ARMC 29	335	ND
dexamethasone	1958	FDA		ND
docetaxel	1995	ARMC 31	341	ND
dromostanolone	1961	FDA		ND
elliptinium acetate	1983	P091123		ND
epirubicin HCI	1984	ARMC 20	318	ND
eribulin	2010	I 287199		ND
estramustine	1980	FDA		ND
ethinyl estradiol	pre-1970	Cole		ND
etoposide	1980	FDA		ND
etoposide phosphate	1996	DNP 10	13	ND
exemestane	1999	DNP 13	46	ND
fluoxymesterone	pre-1970	Cole		ND
formestane	1993	ARMC 29	337	ND
fosfestrol	pre-1977	Carter		ND
fulvestrant	2002	ARMC 38	357	ND
gemtuzumab ozogamicin	2000	DNP 14	23	ND
hexyl aminolevulinate	2004	I 300211		ND
histrelin	2004	I 109865		ND
hydroxyprogesterone	pre-1970	Cole		ND
idarubicin hydrochloride	1990	ARMC 26	303	ND
irinotecan hydrochloride	1994	ARMC 30	301	ND
ixabepilone	2007	ARMC 43	473	ND
medroxyprogesterone acetate	1958	FDA		ND
megesterol acetate	1971	FDA		ND
methylprednisolone	1955	FDA		ND
methyltestosterone	1974	FDA		ND
mifamurtide	2010	DNP 23	18	ND
miltefosine	1993	ARMC 29	340	ND
mitobronitol	1979	FDA		ND
nadrolone phenylpropionate	1959	FDA		ND
norethindrone acetate	pre-1977	Carter		ND
pirarubicin	1988	ARMC 24	309	ND
pralatrexate	2009	DNP 23	18	ND
prednisolone	pre-1977	Carter		ND
prednisone	pre-1970	Cole		ND
talaporfin sodium	2004	ARMC 40	469	ND
temsirolimus	2007	ARMC 43	490	ND
teniposide	1967	FDA		ND
testolactone	1969	FDA		ND
topotecan HCl	1996	ARMC 32	320	ND
trastuzumab emtansine	2013	DT 50(1)	69	ND
triamcinolone	1958	FDA		ND
triptorelin	1986	I 090485		ND
valrubicin	1999	ARMC 35	350	ND
vapreotide acetate	2004	I 135014		ND

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 10. continued

generic name	year introduced	reference	page	source
vindesine	1979	FDA		ND
vinflunine	2010	I 219585		ND
vinorelbine	1989	ARMC 25	320	ND
zinostatin stimalamer	1994	ARMC 30	313	ND
amsacrine	1987	ARMC 23	327	S
arsenic trioxide	2000	DNP 14	23	S
bisantrene hydrochloride	1990	ARMC 26	300	S
busulfan	1954	FDA		S
carboplatin	1986	ARMC 22	318	S
carmustine (BCNU)	1977	FDA		S
chlorambucil	1956	FDA		S
chlortrianisene	pre-1981	Boyd		S
cis-diamminedichloroplatinum	1979	FDA		S
cyclophosphamide	1957	FDA		S
dacarbazine	1975	FDA		S
diethylstilbestrol	pre-1970	Cole		S
flutamide	1983	ARMC 19	318	S
fotemustine	1989	ARMC 25	313	S
heptaplatin/SK-2053R	1999	ARMC 35	348	S
hexamethylmelamine	1979	FDA		S
hydroxyurea	1968	FDA		S
ifosfamide	1976	FDA		S
levamisole	pre-1981	Boyd		S
lobaplatin	1998	DNP 12	35	S
lomustine (CCNU)	1976	FDA		S
lonidamine	1987	ARMC 23	337	S
mechlorethanamine	1958	FDA		S
melphalan	1961	FDA		S
miriplatin hydrate	2010	DNP 23	17	S
mitotane	1970	FDA		S
nedaplatin	1995	ARMC 31	347	S
nilutamide	1987	ARMC 23	338	S
nimustine hydrochloride	pre-1981	Boyd		S
oxaliplatin	1996	ARMC 32	313	S
pamidronate	1987	ARMC 23	326	S
pipobroman	1966	FDA		S
plerixafor hydrochloride	2009	DNP 22	17	S
porfimer sodium	1993	ARMC 29	343	S
procarbazine	1969	FDA		S
ranimustine	1987	ARMC 23	341	S
razoxane	pre-1977	Carter		S
semustine (MCCNU)	pre-1977	Carter		S
sobuzoxane	1994	ARMC 30	310	S
sorafenib	2005	DNP 19	45	S
thiotepa	1959	FDA		S
triethylenemelamine	pre-1981	Boyd		S
zoledronic acid	2000	DNP 14	24	S
alectinib hydrochloride	2014	DT 51(1)	56	S/NM
anastrozole	1995	ARMC 31	338	S/NM
apatinib mesylate	2014	DT 51(1)	56	S/NM
bicalutamide	1995	ARMC 31	338	S/NM
bortezomib	2003	ARMC 39	345	S/NM
camostat mesylate	1985	ARMC 21	325	S/NM
dasatinib	2006	DNP 20	27	S/NM
enzalutamide	2012	I 438422		S/NM
erlotinib hydrochloride	2004	ARMC 40	454	S/NM
fadrozole HCl	1995	ARMC 31	342	S/NM
gefitinib	2002	ARMC 38	358	S/NM
imatinib mesilate	2001	DNP 15	38	S/NM
lapatinib ditosylate	2007	ARMC 43	475	S/NM
letrazole	1996	ARMC 32	311	S/NM

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 10. continued

generic name	year introduced	reference	page	source
nafoxidine	pre-1977	Carter		S/NM
nilotinib hydrochloride	2007	ARMC 43	480	S/NM
pazopanib	2009	DNP 23	18	S/NM
sunitinib malate	2006	DNP 20	27	S/NM
tamoxifen	1973	FDA		S/NM
temoporfin	2002	I 158118		S/NM
toremifene	1989	ARMC 25	319	S/NM
aminoglutethimide	1981(?)	FDA		S*
azacytidine	2004	ARMC 40	447	S*
capecitabine	1998	ARMC 34	319	S*
carmofur	1981	I 091100		S*
clofarabine	2005	DNP 19	44	S*
cytosine arabinoside	1969	FDA		S*
decitabine	2006	DNP 20	27	S*
doxifluridine	1987	ARMC 23	332	S*
enocitabine	1983	ARMC 19	318	S*
floxuridine	1971	FDA		S*
fludarabine phosphate	1991	ARMC 27	327	S*
fluorouracil	1962	FDA		S*
ftorafur	1972	FDA		S*
gemcitabine HCl	1995	ARMC 31	344	S*
mercaptopurine	1953	FDA		S*
methotrexate	1954	FDA		S*
mitoxantrone HCI	1984	ARMC 20	321	S*
nelarabine	2006	ARMC 42	528	S*
pixantrone dimaleate	2012	I 197776		S*
thioguanine	1966	FDA		S*
tipiracil hydrochloride	2014	DT 51(1)	58	S*
uracil mustard	1966	FDA		S*
abarelix	2004	ARMC 40	446	S*/NM
afatinib	2013	DT 50(1)	69	S*/NM
axitinib	2012	I 38296		S*/NM
belinostat	2014	DT 51(1)	56	S*/NM
bexarotene	2000	DNP 14	23	S*/NM
bosutinib	2012	I 301996		S*/NM
cabozantinib S-malate	2012	I 301996		S*/NM
crizotinib	2012	I 379934		S*/NM
dabrafenib mesilate	2011	DT 48(1)	45	S*/NM
degarelix	2009	DNP 22	16	S*/NM
ibrutinib	2013	DT 50(1)	71	S*/NM
idelalisib	2014	DT 51(1)	54	S*/NM
pemetrexed disodium	2004	ARMC 40	463	S*/NM
ponatinib	2013	DT 50(1)	70	S*/NM
radotinib	2012	I 395674		S*/NM
raltiterxed	1996	ARMC 32	315	S*/NM
regorafenib	2012	I 395674		S*/NM
ruxolitinib phosphate	2011	DT 48(1)	47	S*/NM
tamibarotene	2005	DNP 19	45	S*/NM
Temozolomide	1999	ARMC 35	350	S*/NM
trametinib DMSO	2013	DT 50(1)	69	S*/NM
vandetanib	2011	DT 48(1)	45	S*/NM
vemurafenib	2011	DT 48(1)	45	S*/NM
vorinostat	2006	DNP 20	27	S*/NM
autologous tumor cell-BCG	2008	DNP 22	17	V
bcg live	1990	DNP 04	104	V
Cervarix (trade name)	2007	I 309201		V
melanoma theraccine	2001	DNP 15	38	V
vitespen	2008	DNP 22	17	V

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Table 11. Antidiabetic Drugs from 01.01.1981 to 12.31.2014 Organized Alphabetically by Generic Name within Source/Year

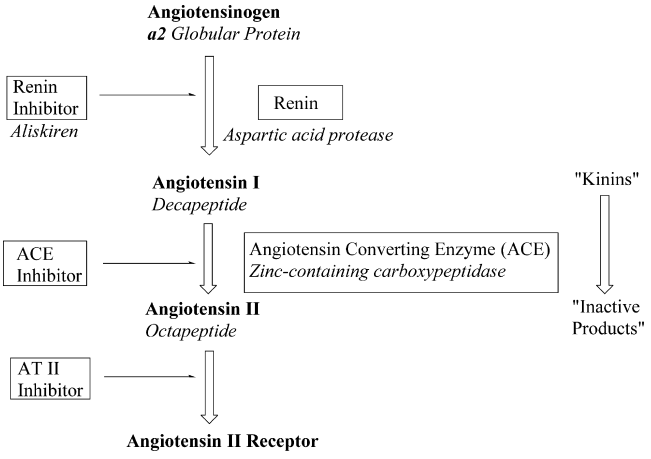
generic name	trade name	year introduced	volume	page	source
isophane insulin	Humulin N	1982	I 091583		B
porcine isophane insulin	Pork Insulatard	1982	I 302757		B
human insulin Zn suspension	Humulin L	1985	I 302828		B
human insulin zinc suspension	Humulin Zn	1985	I 091584		B
soluble insulin	Velosulin BR	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
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
glimepiride	Amaryl	1995	ARMC 31	344	S
repaglinide	Prandin	1998	ARMC 34	329	S
pioglitazone NCl	Actos	1999	ARMC 35	346	S
mitiglinide calcium hydrate	Glufast	2004	ARMC 40	460	S
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 hydrobromide	Tenelia	2012	I 343981		S/ NM
anagliptin	Suiny	2012	I 426247		S/ NM
tolrestat	Alredase	1989	ARMC 25	319	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

Antifungal Agents. In this area, two drugs were approved in the 2011 to 2014 time frame. These were two synthetic compounds, one the azole antifungal efinaconazole (**22**) ,and the other, tavaborole (**23**), is the first example of this novel skeleton containing boron. It should be noted, however, that a natural product, boromycin, a complex macrolide first isolated from *Streptomyces antibioticus*, was reported by the Zahner group[125] in 1967 with antibacterial activity, and then in 1996, it was reisolated by Kohno et al.[126] as an anti-HIV agent from an unspeciated streptomycete. Its probable mode of action is as a specialized ionophore. In contrast to the antibacterial agents, the majority of antifungal agents in the years from 1981 to 2014 are synthetic in origin, as can be seen from inspection of Table 8, with 28 of the 31 approved drugs (90%) being classified as other than natural product based. The paucity of natural product sources can be seen in the modern treatment regimens that still use agents such as amphotericin and griseofulvin, which are both listed in the *Integrity* database as being launched in 1958.

Antiviral Drugs. In this area, as mentioned earlier, a significant number of the agents are vaccines, predominately directed against various serotypes of influenza, as would be expected from the avian flu outbreaks. In the time frame 2011 to 2014, and looking only at small molecules, 16 drugs were approved for basically two viral diseases, HIV, as would be expected, and hepatitis C (HCV), with drugs directed against specific RNA polymerases and HCV proteases. There were no drugs formally from the "N*" categories, but eight fell into the "S*" or "S*/NM" classifications. In 2011, two "S*/NM" drugs were approved, boceprevir (**24**) and telaprevir (**25**), both directed against HCV proteases. None in this classification were approved in 2012. However, as mentioned above, in 2013 one "S*" drug, sofosbuvir (**14**), was approved for use against HCV. This particular drug, a "masked nucleotide", has the potential to

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Scheme 1



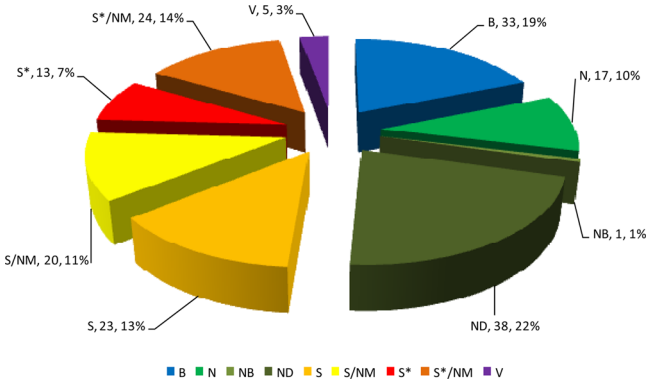
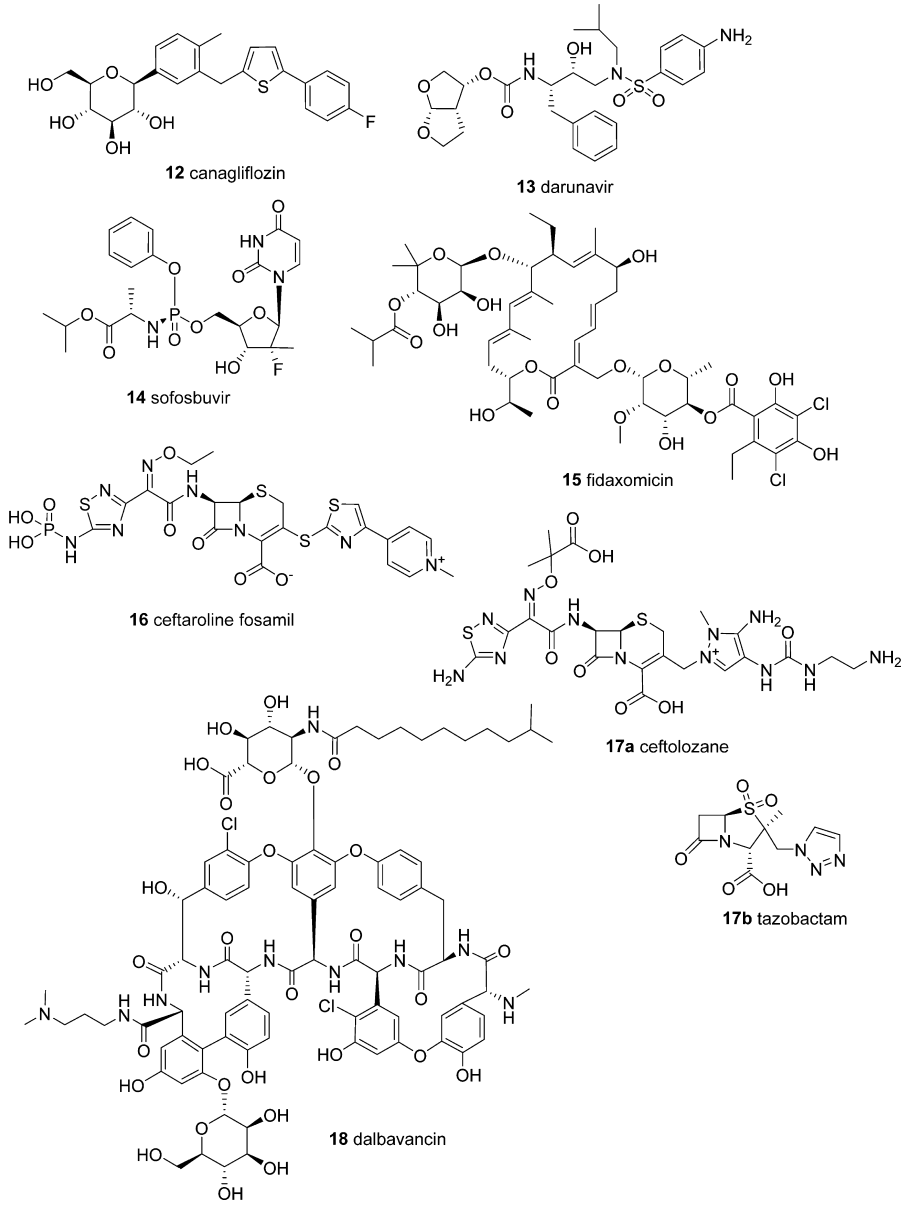


Figure 8. All anticancer drugs 1981−2014; n = 174.

become the best-selling drug of all time, as it currently is the only drug that cures HCV infections in roughly two months. However, its current nominal cost for this treatment is close to

Chart 2



DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

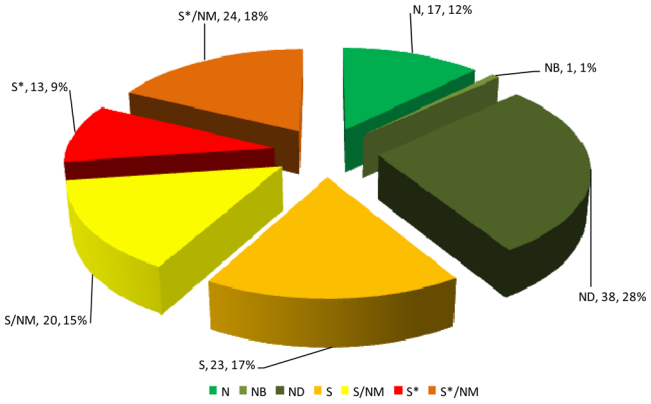


Figure 9. Small-molecule anticancer drugs 1940s–2014; n = 136.

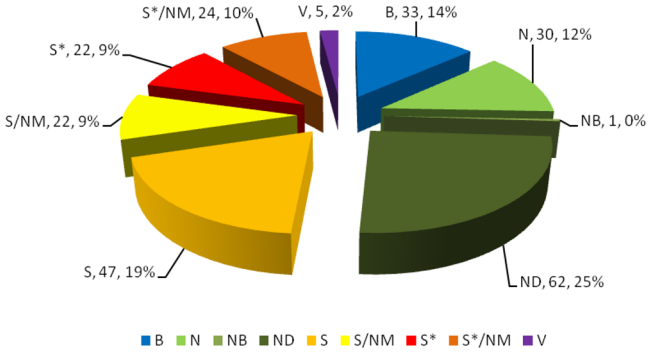


Figure 10. All anticancer drugs 1940s–2014 by source; n = 246.

$90 000 per patient. The only other curative treatment for patients with HCV once a severe stage is reached is a liver transplant. Also in the same year, the "S*/NM" classified drug simeprevir (**26**) was approved and acts against HCV proteases.

In 2014, however, there was a relative flood of approvals including one very unusual action by the FDA. The outlier, before this action is covered, was the approval of the anti-influenza small-molecule drug favipiravir (**27**). In 2014, the FDA approved a combination therapy known as Viekira Pak against HCV proteases. Normally, this combination therapy would not have been included in the listings, but in this case, the FDA effectively approved two clinical candidates, ombitasvir (**28**), then in phase II, and paritaprevir (**29**), then in phase III, in a combination with the 1996-approved drug ritonavir (**30**), also a compound falling into the "S*/NM" classification. Finally, under this category, the HCV protease inhibitor vaniprevir (**31**) was also approved in 2014.

If we now move to the synthetic area for the time period 2011 to 2014, there were five drugs in the "S" classification and three in the "S/NM" classification. In the "S" classification, there was one approval in 2011 of rilpivirine (**32**), a reverse-transcriptase inhibitor, and none in 2012, but in 2013 there were two drugs approved as HIV integrase inhibitors, dolutegravir (**33**) and elvitegravir (**34**). Then, in 2014, two more anti-HCV drugs, daclatasvir (**35**) and dasabuvir (**36**), were approved. Under the "S/NM" classification, three drugs were approved, none in 2011 and 2012, one [cobicistat (**37**)] in 2013 as an HIV protease inhibitor, and then two anti-HCV drugs in 2014, asunaprevir (**38**) and ledipasvir (**39**). The latter drug is unusual in that it is part of a combination therapy with sofosbuvir (**14**) under the trade name Harvoni and thus may be in direct competition with the earlier drug.

To sum up, in contrast to the antibacterial and antifungal areas, in the antiviral case, as shown in Table 7, small molecules accounted for 64 drugs, with only four (or 6%) in the 34 years of coverage falling into the "ND" category. However, as mentioned earlier, we have consistently placed modified nucleosides, peptidomimetics, etc., into the "S*" or "S*/NM" category. If these are added to the four drugs mentioned above, then the other than synthetic molecules account for 45, or 70% overall.

Disease Areas without Current Natural Product Drugs. As reported in our earlier analyses,[1−4] there are still disease areas where at the present time the available drugs are totally synthetic in origin. 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 less approved drugs that are also totally synthetic.

Disease Areas with "*/NM" Classified Drugs. As mentioned in our earlier reviews,[2−4] due to the introduction of the "NM" subcategory, indications such as antidepressants,

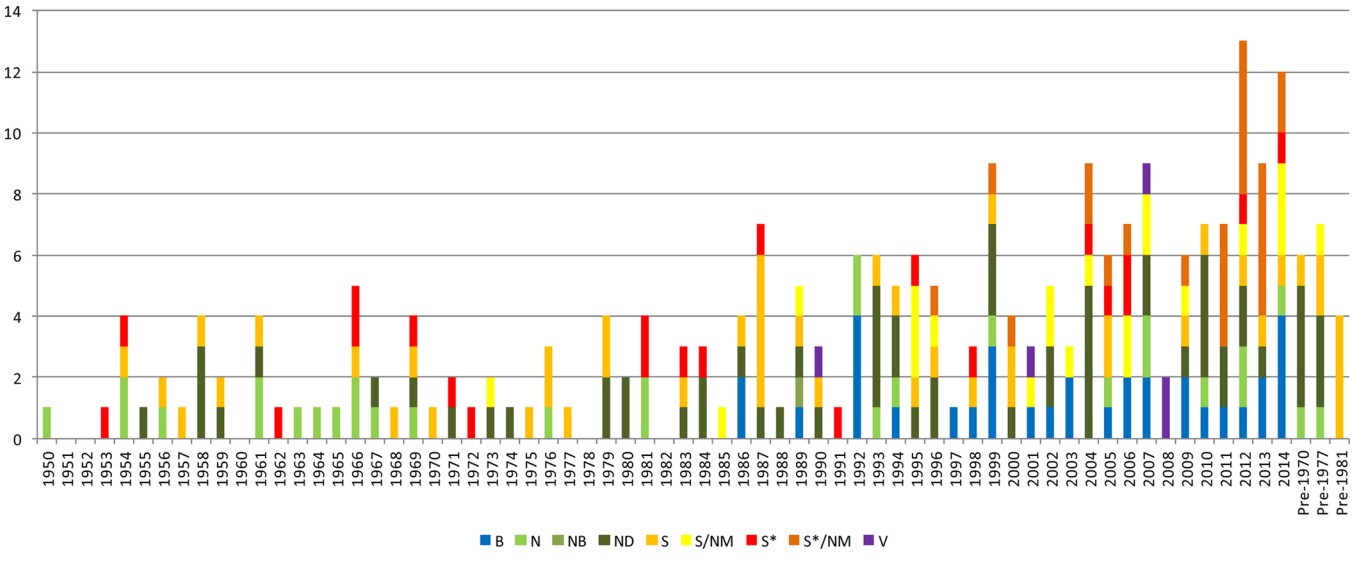
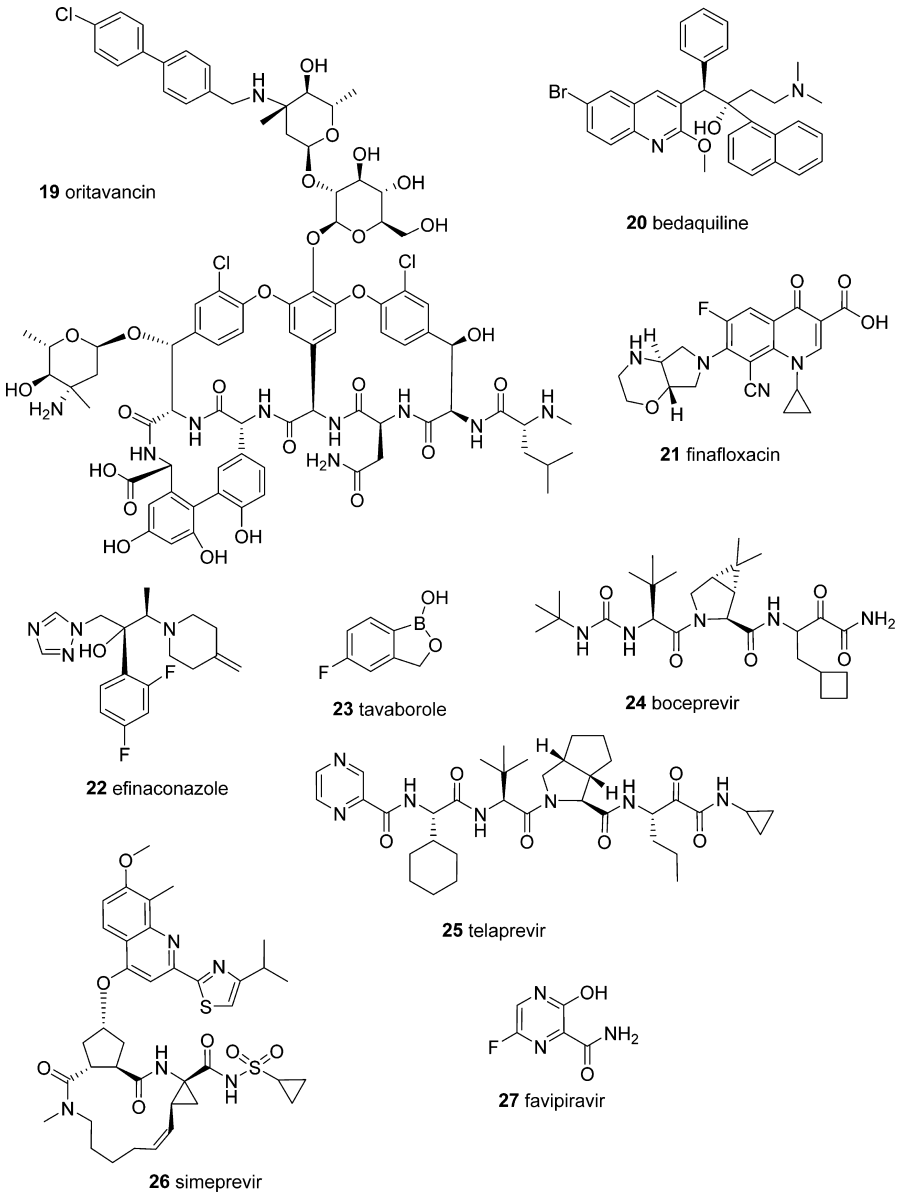


Figure 11. All anticancer drugs 1940s–2014 by source/year; n = 246.

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629–661

Chart 3



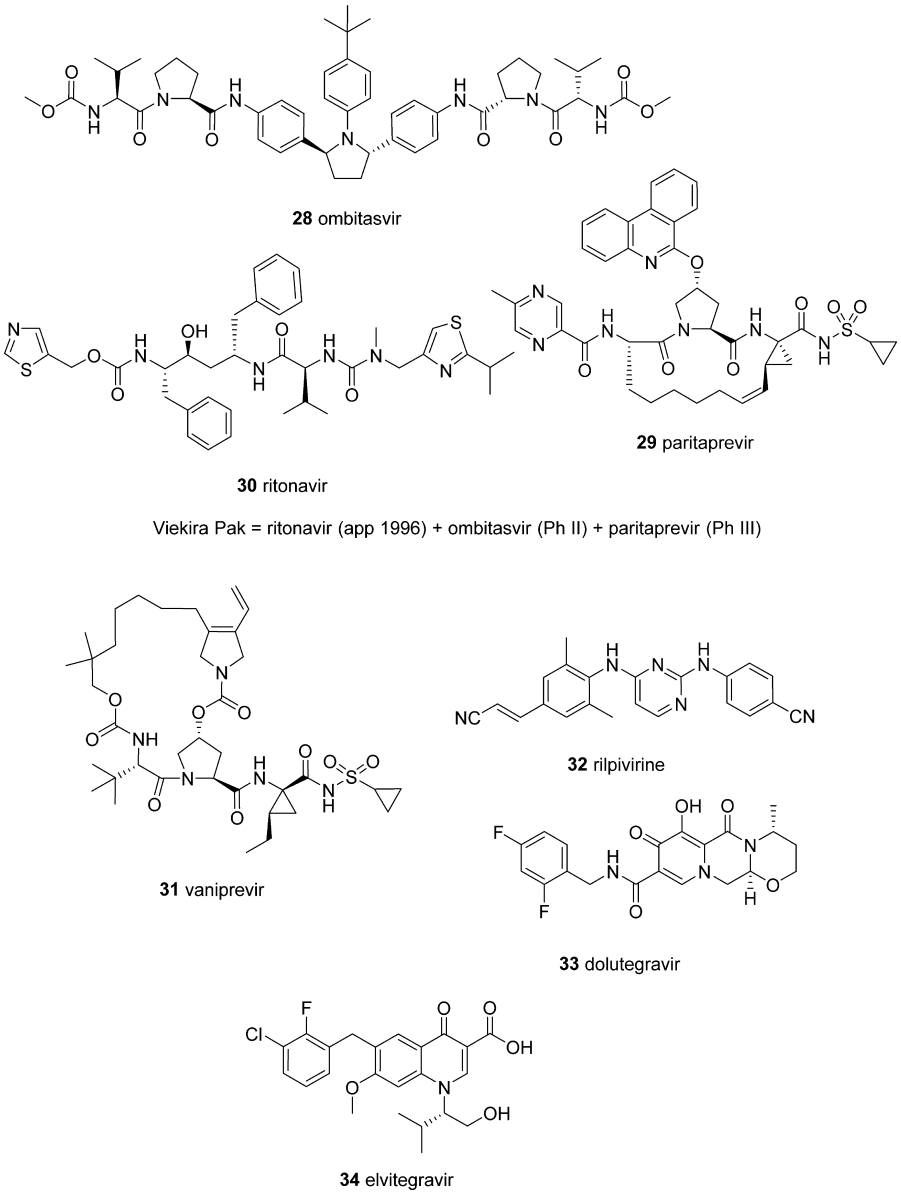
bronchodilators, and cardiotonics now have substantial numbers that, although formally "S" or "S*", fall into the "S/NM" or "S*/NM" subcategory, as the information in the literature points to their interactions at active sites as competitive inhibitors.

Anticancer Drugs 1981−2014. In this disease area (Table 9), in the time frame covered (01/1981−12/2014) there were 174 NCEs in total, with the number of nonbiologicals, aka small molecules, being 136 (78%), effectively the same percentage as the value of 77% in the last review.[4] Using the total of 136 as being equal to 100%, the breakdown was as follows, with the values from the last review inserted for comparison: "N" (17, 13% {11, 11%}), "NB" (1, 1% {1, 1%}), "ND" (38, 28% {32, 32%}), "S" (23, 17%, {20, 20%}), "S/NM" (20, 15% {16, 16% }), "S*" (13, 10% {11, 11%}), and "S*/NM" (24, 18% {8, 8%}). Thus, using our criteria, only 17% of the total number of small-molecule anticancer drugs were classifiable into the "S" (synthetic) category. Expressed as a proportion of the non-biologicals/vaccines, then 113 of 136 (83%) were either natural products *per se* or were based thereon, or mimicked natural products in one form or another.

From a natural products perspective, in the antitumor area there were some significant aspects in the four years from 2011 to 2014. Another nanoparticular, paclitaxel (PICN), was approved in India in 2014 as the fourth variation on this drug delivery approach, and two plant-derived agents, omacetaxine mepesuccinate (homoharringtonine) (**40**) and ingenol mebutate (**41**) (as an agent against actinic keratosis, a precancerous condition, that if untreated usually leads to a melanoma), were approved in 2012 by the FDA. The history of homoharringtonine was described by Camp[127] and Kantarjian et al.,[128] and that of the diterpenoid ingenol by a number of publications from Baran's group,[129−131] all showing the levels to which researchers had gone to develop these agents. From an "ND" aspect, abiraterone[132] (**42**) was approved in 2011 with Adcetris, a dolastatin 10 derivative linked to an anti-CD33 monoclonal,[133,134] being approved the same year. In 2012, the aminolaevulinic acid conjugate Ameluz was approved for photodynamic therapy,[135] and the same year saw the approval of carfilzomib[136] (**43**), the proteasome derivative that evolved from the work of Craig Crews[137] at Yale University. Then, in 2013 the maytansine−herceptin linked monoclonal

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Chart 4



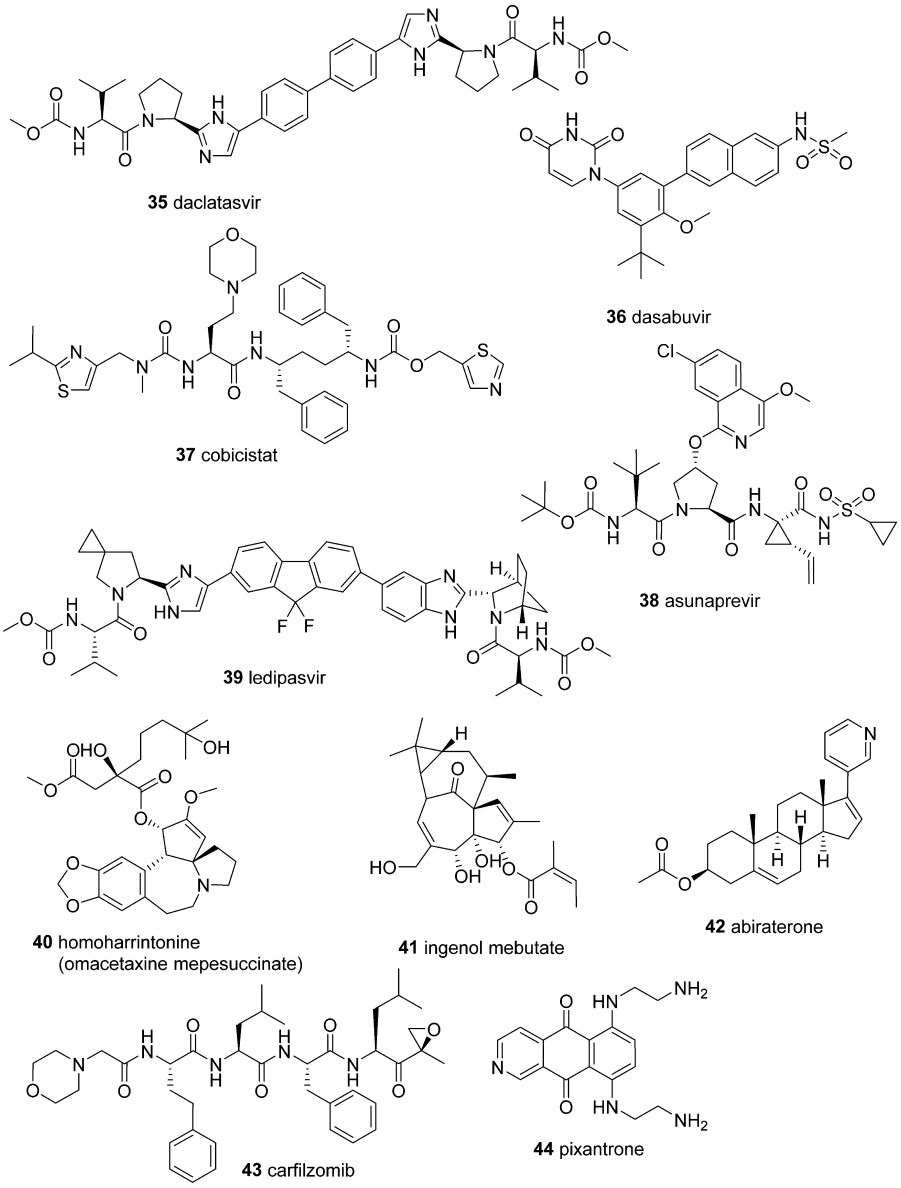
antibody Kadcyla was approved.[138,139] From the "S*" category, pixantrone[140] (**44**) was approved in 2012, with the uridine derivative tipiracil[141] (**45**) approved in 2014. Inspection of Table 9 shows that a significant number of PTKs were also approved in these years, with the numbers being predominately under the "S*/NM" category, although the HDAC inhibitor belinostat[142] (**46**) also was approved in 2014 and fell into the same category; thus the influence of natural products in the synthetic arena is still obvious.

Anticancer Drugs, Late 1930s to 2014. In this current review, we have continued as in our previous contributions[2−4] to reassess the influence of natural products and their mimics as leads to anticancer drugs from the beginnings of antitumor chemotherapy in the very late 1930s to the early 1940s. Using data from the FDA listings of antitumor drugs, plus our earlier data sources and with help from colleagues based worldwide, we have been able to specify the years in which all but 17 of the 246 drugs listed in Table 10 were approved. We then identified these 17 agents by inspection of three time-relevant textbooks on antitumor treatment,[103−105] and these were added to the overall listings using the names of the lead authors as the source citation.

Inspection of Figure 10 and Table 10 shows that, over the whole category of anticancer drugs approved worldwide, the 246 approved agents can be categorized as follows, with the figures for the 2012 review[4] (n = 206) being included for comparison: "B" (33, 13% {26; 13%}), "N" (30, 12% {27; 13%}), "NB" (1, 1% {1; 1%}), "ND" (62, 25% {57; 28%}), "S" (47, 19% {44; 21%}), "S/NM" (22, 9% {18; 9%}), "S*" (22, 9% {20; 10%}), "S*/NM" (24, 10% {8; 4%}), and "V" (5, 2% {5; 2%}). Removing the high-molecular-weight materials (biologicals and vaccines) reduces the overall number to 207 (100%). If we then use the number of nonsynthetics but include the naturally inspired agents (i.e., "N", "ND", "S/NM", "S*", "S*/NM"), this number is 160, or 77% of the total small molecules (having removed categories "B", "NB", and "V" from the overall total), effectively the same percentage as the 75% figure from the 2012 review.[4] If the two "/NM" categories are also removed, then the figure drops to 114, or 55%, compared to the 60% in our earlier reviews. This can be attributed to the large number of protein kinase inhibitors that

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Chart 5



fell into the "/SM" classifications in the last four years, thus increasing the denominator for small molecules. Etoposide phosphate and various nanopaticle formulations of Taxol have been included for the sake of completeness. It should again be pointed out that the 17 antitumor drugs shown on the right in Figure 11 are not duplicated in the rest of the bar graph; we simply have not been able to locate accurate data on their initial approval dates.

Small-Molecule Antidiabetic Drugs. In the case of these drugs and looking only at small molecules for both diabetes I and II, the numbers since our last review have increased by 10 to 29 (Table 11). One, lixisentide (**47**), approved in 2013, fell into the "ND" classification, as it, like extenatide (Byetta), is a derivative of exendin-4.[143] Under the classification "S/NM", there were three approvals of drugs all targeted at the same enzyme complex, dipeptidyl peptidase IV (DPP-IV). The first was linagliptin[144] (**48**) in 2011, with the next two in 2012, teneligliptin[145] (**49**) and anagliptin[146] (**50**).

However, for "pride of place", one cannot beat the six sodium-dependent glucose transporter inhibitors (SGLTi's) that were approved between 2012 and 2014, all falling into the "S*/NM" classification. In 2012, dapagliflozin[147] (**51**) was approved in the EU; this was followed in 2013 by canagliflozin[148] (**12**) in the USA. In 2014, there were no less than four drugs launched all directed against this target. In alphabetical order, they were empaglifozin[149] (**52**) in the EU and the USA almost simultaneously, with the next three, ipragliflozin cocrystallized with L-proline[150] (**53**), luseogliflozin[151] (**54**), and tofoglflozin[152] (**55**), launched in Japan.

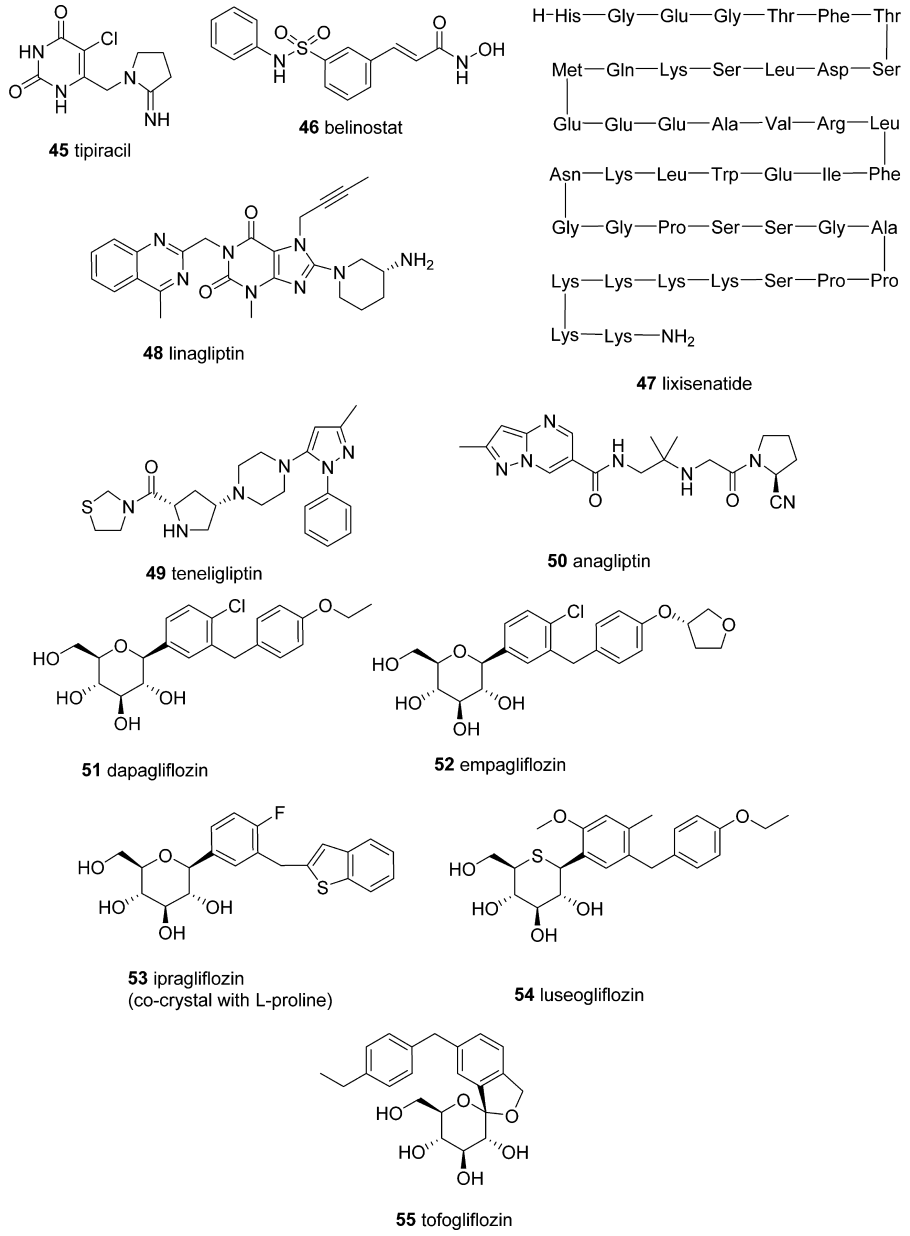
DISCUSSION

In contrast to the situation referred to in our previous three reviews,[2−4] the decline or leveling of the output of the R&D programs of the pharmaceutical companies may have begun to turn around when compared to earlier years in the 21st century. The figures for drugs of all types had dropped in 2006 to 40 NCEs launched, of which 19 (48%) were classified in the "other than small molecules", being in the "B/V" categories.

Increases in Biologicals and Vaccines from 2007. In the eight years 2007−2014 as shown in the bar graph in Figure 2, the

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

Chart 6



corresponding figures are as follows. In 2007, there were 44 NCEs launched, with 18 (41%) classified as "B/V". In 2008, 38 NCEs were launched, with 14 (37%) classified as "B/V". In 2009, 42 NCEs were launched, with 18 (43%) classified as "B/V". Then, in 2010, there was a dip, where only 33 NCEs were launched, with 13 (39%) classified as "B/V". In 2011, there was an increase of 1 to 34, with 7 (20%) classified as "B/V"; however the proportion of small molecules increased that year, so the divisor increased. In 2012, there was almost a doubling of NCEs to 60, but 25 (42%) fell into the "B/V" categories. This increase in 2012 in approved vaccines was due predominately to "avian influenza" treatments. In 2013, there was a drop to 47 NCEs, with 16 (34%) still attributable to the "B/V" categories. However, in 2014, the trend line for small-molecule NCEs began to move upward again, with 65 NCEs approved, of which 21 (32%) were in the "B/V" categories. Thus, one can see that, overall, of the total of 363 NCEs in these years, 132 (36%) fell into the "B/V" categories. However, as shown in Figure 7, although there were fluctuations in the overall numbers, a reasonable to substantial proportion of all small-molecule NCEs fell into the "N*" category; thus even in these days of advances in immunopharmacology-based treatments, natural-product-based small molecules are still in play.

Potential Sources of Natural Product Skeletons. Although combinatorial chemistry continues to play a major role in the drug development process, as mentioned earlier, it is noteworthy that the trend toward the synthesis of complex natural-product-like libraries has continued. Even including these newer methodologies, we still cannot find other *de novo* combinatorial compounds approved anywhere in the world than the three compounds (**1**–**3**) referred to earlier, although reliable data are still not available on approvals in Russia and the People's Republic of China at this time.

A rapid analysis of the small-molecule entities approved from 2011 to 2014 has indicated that there were significant numbers of antitumor, antibacterial, and antifungal agents approved, as

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629–661

mentioned above. The antibacterial compounds were either NPs or based on their skeletons, although, as is now, "the norm" antifungal agents were synthetic in origin.

Genomic Sources of Novel NP Skeletons. If one asks the question "where will novel natural product skeletons come from in the future?", the answer, we think, is from the massive amounts of genetic information now being amassed from microbial sources. There was always the comment made in previous years that only a very small proportion of the microbial world can be fermented. However, two excellent papers in the last two years have shown that genetic information can be "abstracted" from as yet uncultured microbes from sessile marine organisms. These were the "tour de force" by the Piel group in 2014, demonstrating that 31 of the then 32 known bioactive metabolites from the sponge *Theonella swinhoei* Y (yellow variant) were produced by a totally novel biochemical mechanism in an as yet uncultured microbe.[153] This was followed a year later by proof in the middle of 2015 from the Sherman group[154] that the source of the approved antitumor drug Yondelis, or Et743, is an as yet uncultured microbe in the tunicate *Ecteinascidia turbinata*, from which the Et743 complex was first isolated. Does this mean only from invertebrate sources? No, we consider that the information now coming from investigations on free-living microbes from often extreme sources (cold, hot, high pressure, etc.) will also provide novel skeletons for further work.[5,8−11]

Similarly, if one moves to the plant kingdom, there is now a significant volume of published work that indicates that a fair number of what were thought to be "plant-derived" natural products are in fact produced "in part" and in some cases, such as maytansine, totally[155,156] by interactions with endophytic microbes, frequently fungi. We currently say "in part" because the evidence for total production only by the isolated microbe is not yet finalized, and one cannot rule out horizontal gene transfer at this moment. However, the recent work by the Oberlies group[157] on the production of silybins by an endophytic fungus from the leaves of the milk thistle *Silybum marianum* demonstrated that these metabolites were produced by the isolated fungus when supplemented by a sterilized extract from the plant, a supplementation strategy well known in the days of antibiotic discovery but generally not used today by newer investigators studying these types of systems. People interested in this aspect of microbiology should also read the recent article from the Spiteller group demonstrating the production of cyclopeptides by a *Fusarium* species as "cross-talk" agents in plants, as this demonstrates the type of interaction we are referring to.[158]

Very recently, a series of reviews in the journal *Natural Product Reports* have further demonstrated the capabilities of modern techniques to help unlock the genomes of both cultivatable and "as yet uncultured" microbes from all sources. These should be read in conjunction with the articles referred to above on microbes isolated from marine invertebrates and plants, since together these aptly demonstrate the new technologies that can be brought to bear on the search for novel scaffolds from nature.[159−162]

In the period since our last review, other authors prominent in the natural product community have also published excellent reviews on natural products as drugs,[163,164] and these, together with the review by Butler et al.,[165] on natural product-based compounds in clinical trials, should also be read in conjunction with this review. In addition there were two very interesting reviews on small molecules, including natural products and close relatives, as protein−protein interaction inhibitors, which we also recommend reading to see how the role of NPs has expanded.[166,167]

That synthetic chemists are not letting opportunities go by can be seen from the 2014 essay by Nicolaou[168] and a series of papers that cover synthetic approaches to the new drugs from 2009 to 2013.[169−173] It is highly probable that in the near future totally synthetic variations on complex natural products will be part of the therapeutic arsenal used by physicians. One has only to look at the extremely elegant syntheses of complex natural products reported recently by Baran and his co-workers to visualize the potential of coupling very active and interesting natural products with the skills of synthetic chemists in academia and industry.[131]

Two recent papers of interest to drug discovery and development that are quite relevant to the discussion are as follows. The first, which is quite sobering to read, intimates, with data, that the actual productivity of the pharmaceutical industry from a development aspect is lower than is evident from the press releases and other outlets that are often used to demonstrate success.[174] The second may be quite beneficial as far as natural products and/or their derivatives are concerned, as it now appears that phenotypic screening using high-content methodologies may be making a comeback over "targeted screening systems".[175]

It is often not fully appreciated that the major hurdle in bringing a natural-product-based complex molecule to market is not the isolation, basic semisynthesis, or total synthesis, but the immense supply problems faced by process chemists in translating research laboratory discoveries to commercial items. Some recent examples of how these problems were overcome with natural products or their derivatives are given in a recent short review by one of the present authors.[176]

In this review, as we stated in 2003, 2007, and 2012,[2−4] we have *yet again* demonstrated that natural products play a dominant role in the discovery of leads for the development of drugs for the treatment of human diseases. As we mentioned in earlier articles, some of our colleagues argued (though not in press, only in personal conversations at various fora) that the introduction of categories such as "S/NM" and "S*/NM" may well cause an overstatement of the role played by natural products in the drug discovery process. On the contrary, we would still argue that these further serve to illustrate the inspiration provided by Nature to receptive organic chemists in devising ingenious syntheses of structural mimics to compete with Mother Nature's longstanding substrates. Even if we discount these categories, the continuing and overwhelming contribution of natural products to the expansion of the chemotherapeutic armamentarium is clearly evident, as demonstrated in Figures 6 and 7, and as we stated in our earlier papers, much of Nature's "treasure trove of small molecules" remains to be explored, particularly from the marine and microbial environments.

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

Finally, the award of half of the 2015 Nobel Prize for Physiology or Medicine to Drs. Ŏmura and Campbell for their discovery and development of the avermectin/ivermectin complexes, with the other half being awarded to Prof. Tu for

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

her discovery and development of artemisinin, is truly excellent news for the general public, as they may now begin to understand where these significant drugs were sourced. Two very recent publications cover some of the work that led to the awarding of this Nobel prize. The first by McKerrow[177] is a short description of the work performed by the three scientists, and the second, by Wang et al.,[178] demonstrates the multiplicity of targets in the malaria parasite *Plasmodium falciparum* for artemisinin, none of which would have been recognized but for this agent.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jnatprod.5b01055.

The drug data set (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: djnewman664@verizon.net.

Notes

The authors declare no competing financial interest.

No external funding was provided to the authors from any source. All analyses of data were performed subsequent to the formal retirement of the corresponding author from the NCI on January 10, 2015. Both authors, though retired from NCI, are still NIH Special Volunteers.

■ DEDICATION

Dedicated to Professors John Blunt and Murray Munro, of the University of Canterbury, for their pioneering work on bioactive marine natural products.

■ REFERENCES

(1) Cragg, G. M.; Newman, D. J.; Snader, K. M. *J. Nat. Prod.* **1997**, *60*, 52−60.
(2) Newman, D. J.; Cragg, G. M.; Snader, K. M. *J. Nat. Prod.* **2003**, *66*, 1022−1037.
(3) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461−477.
(4) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311−335.
(5) Cragg, G. M.; Newman, D. J. *Biochim. Biophys. Acta, Gen. Subj.* **2013**, *1830*, 3670−3695.
(6) Newman, D. J.; Giddings, L.-A. *Phytochem. Rev.* **2014**, *13*, 123−137.
(7) Newman, D. J.; Cragg, G. M. In *Macrocycles in Drug Discovery; RSC Drug Discovery Series No. 40*; Levin, J., Ed.; Royal Society of Chemistry: Cambridge, UK, 2014; pp 1−36.
(8) Giddings, L.-A.; Newman, D. J. *Bioactive Compounds from Terrestrial Extremophiles*; Springer: Heidelberg, 2015.
(9) Giddings, L.-A.; Newman, D. J. *Bioactive Compounds from Marine Extremophiles*; Springer: Heidelberg, 2015.
(10) Giddings, L.-A.; Newman, D. J. *Bioactive Compounds from Extremophiles, Genomic Studies*; Springer: Heidelberg, 2015.
(11) Newman, D. J.; Cragg, G. M.; Kingston, D. G. I. In *The Practice of Medicinal Chemistry*, 4th ed.; Wermuth, C. G.; Aldous, D.; Raboisson, P.; Rognan, D., Eds.; Elsevier: Amsterdam, 2015; pp 101−139.
(12) Pelish, H. E.; Westwood, N. J.; Feng, Y.; Kirchausen, T.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 6740−6741.
(13) Spring, D. R. *Org. Biomol. Chem.* **2003**, *1*, 3867−3870.
(14) Burke, M. D.; Schreiber, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 46−58.
(15) Zhonghong, G.; Reddy, P. T.; Quevillion, S.; Couve-Bonnaire, S.; Ayra, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1366−1368.
(16) Dandapani, S.; Marcaurelle, L. A. *Curr. Opin. Chem. Biol.* **2010**, *14*, 362−370.
(17) Reayi, A.; Arya, P. *Curr. Opin. Chem. Biol.* **2005**, *9*, 240−247.
(18) Keller, T. H.; Pichota, A.; Yin, Z. *Curr. Opin. Chem. Biol.* **2006**, *10*, 357−361.
(19) Lipinski, C. A. *Drug Discovery Today: Technol.* **2004**, *1*, 337−341.
(20) Macarron, R. *Drug Discovery Today* **2006**, *11*, 277−279.
(21) Koehn, F. E. *MedChemComm* **2012**, *3*, 854−865.
(22) Doak, B. C.; Over, B.; Giordanetto, F.; Kihlberg, J. *Chem. Biol.* **2014**, *21*, 1115−1142.
(23) Camp, D.; Garavelas, A.; Campitelli, M. *J. Nat. Prod.* **2015**, *78*, 1370−1382.
(24) Macarron, R.; Banks, M. N.; Bojanic, D.; Burns, D. J.; Cirovic, D. A.; Garyantes, T.; Green, D. V. S.; Hertzberg, R. P.; Janzen, W. P.; Paslay, J. W.; Schopfer, U.; Sittampalam, G. S. *Nat. Rev. Drug Discovery* **2011**, *10*, 188−195.
(25) Macarron, R. *Nat. Chem. Biol.* **2015**, *11*, 904−905.
(26) Wassermann, A. M.; Lounkine, E.; Hoepfner, D.; Le Goff, G.; King, F. J.; Studer, C.; Peltier, J. M.; Grippo, M. L.; Prindle, V.; Tao, J.; Schuffenhauer, A.; Wallace, I. M.; Chen, S.; Krastel, P.; Cobos-Correa, A.; Parker, C. N.; Davies, J. W.; Glick, M. *Nat. Chem. Biol.* **2015**, *11*, 958−966.
(27) Bisson, J.; McAlpine, J. B.; Friesen, J. B.; Chen, S.-N.; Graham, J.; Pauli, G. F. *J. Med. Chem.* **2015**, DOI: 10.1021/acs.jmedchem.5b01009.
(28) Baell, J.; Walters, M. A. *Nature* **2014**, *513*, 481−483.
(29) Erlanson, D. A. *J. Med. Chem.* **2015**, *58*, 2088−2090.
(30) Ryan, N. J. *Drugs* **2014**, *74*, 1709−1714.
(31) Hoelder, S.; Clarke, P. A.; Workman, P. *Mol. Oncol.* **2012**, *6*, 155−176.
(32) Bergmann, W.; Feeney, R. J. *J. Am. Chem. Soc.* **1950**, *72*, 2809−2810.
(33) Bergmann, W.; Feeney, R. J. *J. Org. Chem.* **1951**, *16*, 981−987.
(34) Bergmann, W.; Burke, D. C. *J. Org. Chem.* **1955**, *20*, 1501−1507.
(35) Bertin, M. J.; Schwartz, S. L.; Lee, J.; Korobeynikov, A.; Dorrestein, P. C.; Gerwick, L.; Gerwick, W. H. *J. Nat. Prod.* **2015**, *78*, 493−499.
(36) Szychowski, J.; Truchon, J.-F.; Bennani, Y. L. *J. Med. Chem.* **2014**, *57*, 9292−9308.
(37) Bathula, S. R.; Akondi, S. M.; Mainkar, P. S.; Chandrasekhar, S. *Org. Biomol. Chem.* **2015**, *13*, 6432−6448.
(38) Thaker, M. N.; Wright, G. D. *ACS Synth. Biol.* **2015**, *4*, 195−206.
(39) Stockdale, T. P.; Williams, C. M. *Chem. Soc. Rev.* **2015**, *44*, 7737−7763.
(40) Yoganathan, S.; Miller, S. J. *J. Med. Chem.* **2015**, *58*, 2367−2377.
(41) Novaes, L. F. T.; Avila, C. M.; Pelizzaro-Rocha, K. J.; Vendramini-Costa, D. B.; Dias, M. P.; Trivella, D. B. B.; de Carvalho, J. E.; Ferreira-Halder, C. V.; Pilli, R. A. *ChemMedChem* **2015**, *10*, 1687−1699.
(42) Nicolaou, K. C. *Chem. Biol.* **2014**, *21*, 1039−1045.
(43) Allen, R. C. In *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic Press: Orlando, 1984; Vol. *19*, pp 313−326.
(44) Allen, R. C. In *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic Press: Orlando, 1985; Vol. *20*, pp 315−325.
(45) Allen, R. C. In *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic Press: Orlando, 1986; Vol. *21*, pp 323−335.
(46) Allen, R. C. In *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic Press: Orlando, 1987; Vol. *22*, pp 315−330.
(47) Ong, H. H.; Allen, R. C. In *Annual Reports in Medicinal Chemistry*; Allen, R. C., Ed.; Academic Press: San Diego, 1988; Vol. *23*, pp 325−348.
(48) Ong, H. H.; Allen, R. C. In *Annual Reports in Medicinal Chemistry*; Allen, R. C., Ed.; Academic Press: San Diego, 1989; Vol. *24*, pp 295−315.
(49) Ong, H. H.; Allen, R. C. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1990; Vol. *25*, pp 309−322.
(50) Strupczewski, J. D.; Ellis, D. B.; Allen, R. C. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1991; Vol. *26*, pp 297−313.
(51) Strupczewski, J. D.; Ellis, D. B. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1992; Vol. *27*, pp 321−337.

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

(52) Strupczewski, J. D.; Ellis, D. B. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1993; Vol. *28*, pp 325−341.
(53) Cheng, X.-M. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1994; Vol. *29*, pp 331−354.
(54) Cheng, X.-M. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1995; Vol. *30*, pp 295−317.
(55) Cheng, X.-M. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1996; Vol. *31*, pp 337−355.
(56) Galatsis, P. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1997; Vol. *32*, pp 305−326.
(57) Galatsis, P. In *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed.; Academic Press: San Diego, 1998; Vol. *33*, pp 327−353.
(58) Gaudilliere, B. In *Annual Reports in Medicinal Chemistry*; Doherty, A. M., Ed.; Academic Press: San Diego, 1999; Vol. *34*, pp 317−338.
(59) Gaudilliere, B.; Berna, P. In *Annual Reports in Medicinal Chemistry*; Doherty, A. M., Ed.; Academic Press: San Diego, 2000; Vol. *35*, pp 331−355.
(60) Gaudilliere, B.; Bernardelli, P.; Berna, P. In *Annual Reports in Medicinal Chemistry*; Doherty, A. M, Ed.; Academic Press: San Diego, 2001; Vol. *36*, pp 293−318.
(61) Bernardelli, P.; Gaudilliere, B.; Vergne, F. In *Annual Reports in Medicinal Chemistry*; Doherty, A. M., Ed.; Academic Press: Amsterdam, 2002; Vol. *37*, pp 257−277.
(62) Boyer-Joubert, C.; Lorthiois, E.; Moreau, F. In *Annual Reports in Medicinal Chemistry*; Doherty, A. M., Ed.; Academic Press: Amsterdam, 2003; Vol. *38*, pp 347−374.
(63) Hegde, S.; Carter, J. In *Annual Reports in Medicinal Chemistry*; Doherty, A. M., Ed.; Academic Press: Amsterdam, 2004; Vol. *39*, pp 337−368.
(64) Hegde, S.; Schmidt, M. In *Annual Reports in Medicinal Chemistry*; Doherty, A. M., Ed.; Academic Press: Amsterdam, 2005; Vol. *40*, pp 443−473.
(65) Hegde, S.; Schmidt, M. In *Annual Reports in Medicinal Chemistry*; Wood, A., Ed.; Academic Press: Amsterdam, 2006; Vol. *41*, pp 439−477.
(66) Hegde, S.; Schmidt, M. In *Annual Reports in Medicinal Chemistry*; Macor, J. E., Ed.; Academic Press: Amsterdam, 2007; Vol. *42*, pp 505−554.
(67) Hegde, S.; Schmidt, M. In *Annual Reports in Medicinal Chemistry*; Macor, J. E., Ed.; Academic Press: Amsterdam, 2008; Vol. *43*, pp 455−497.
(68) Hegde, S.; Schmidt, M. In *Annual Reports in Medicinal Chemistry*; Macor, J. E., Ed.; Academic Press: Amsterdam, 2009; Vol. *44*, pp 577−632.
(69) Hegde, S.; Schmidt, M. In *Annual Reports in Medicinal Chemistry*; Macor, J. E., Ed.; Academic Press: Amsterdam, 2010; Vol. *45*, pp 467−537.
(70) Bronson, J.; Dhar, M.; Ewing, W.; Lonberg, N. In *Annual Reports in Medicinal Chemistry*; Macor, J. E., Ed.; Academic Press: Amsterdam, 2011; Vol. *46*, pp 433−502.
(71) Bronson, J.; Dhar, M.; Ewing, W.; Lonberg, N. In *Annual Reports in Medicinal Chemistry*; Desai, M. C., Ed.; Academic Press: Amsterdam, 2012; Vol. *47*, pp 499−569.
(72) Bronson, J.; Black, A.; Dhar, T. G. M.; Ellsworth, B. A.; Merritt, J. R. In *Annual Reports in Medicinal Chemistry*; Desai, M. C., Ed.; Academic Press: Amsterdam, 2013; Vol. *48*, pp 471−546.
(73) Bronson, J.; Black, A.; Dhar, M.; Ellsworth, B.; Merritt, J. R. In *Annual Reports in Medicinal Chemistry*; Desai, M. C., Ed.; Academic Press: Amsterdam, 2014; Vol. *49*, pp 437−508.
(74) Bronson, J.; Black, A.; Dhar, M.; Ellsworth, B. A.; Merritt, J. R.; Peese, K.; Pashine, A. In *2015 Medicinal Chemistry Reviews*; Desai, M. C., Ed.; Medicinal Chemistry Division ACS: Washington DC, 2015; Vol. *50*, pp 461−576.
(75) Prous, J. R. *Drug News Persp.* **1990**, *3*, 19−29.
(76) Prous, J. R. *Drug News Persp.* **1991**, *4*, 96−109.
(77) Prous, J. R. *Drug News Persp.* **1992**, *5*, 93−101.
(78) Prous, J. R. *Drug News Persp.* **1993**, *6*, 95−106.
(79) Prous, J. R. *Drug News Persp* **1994**, *7*, 26−36.
(80) Prous, J. R. *Drug News Persp.* **1995**, *8*, 24−37.
(81) Prous, J. R. *Drug News Persp.* **1996**, *9*, 19−32.
(82) Graul, A. I. *Drug News Persp.* **1997**, *10*, 5−18.
(83) Graul, A. I. *Drug News Persp.* **1998**, *11*, 15−32.
(84) Graul, A. I. *Drug News Persp.* **1999**, *12*, 27−43.
(85) Graul, A. I. *Drug News Persp.* **2000**, *13*, 37−53.
(86) Graul, A. I. *Drug News Persp.* **2001**, *14*, 12−31.
(87) Graul, A. I. *Drug News Persp.* **2002**, *15*, 29−43.
(88) Graul, A. I. *Drug News Persp.* **2003**, *16*, 22−39.
(89) Graul, A. I. *Drug News Persp.* **2004**, *17*, 43−57.
(90) Graul, A. I.; Prous, J. R. *Drug News Persp.* **2005**, *18*, 21−36.
(91) Graul, A. I.; Prous, J. R. *Drug News Persp.* **2006**, *19*, 33−53.
(92) Graul, A. I.; Sorbera, L. A.; Bozzo, J.; Serradell, N.; Revel, L.; Prous, J. R. *Drug News Persp.* **2007**, *20*, 17−44.
(93) Graul, A. I.; Prous, J. R.; Barrionuevo, M.; Bozzo, J.; Castañer, R.; Cruces, E.; Revel, L.; Rosa, E.; Serradell, N.; Sorbera, L. A. *Drug News Persp.* **2008**, *21*, 7−35.
(94) Graul, A. I.; Revel, L.; Barrionuevo, M.; Cruces, E.; Rosa, E.; Vergés, C.; Lupone, B.; Diaz, N.; Castañe, R. *Drug News Perspect.* **2009**, *22*, 7−27.
(95) Graul, A. I.; Sorbera, L. A.; Pina, P.; Tell, M.; Cruces, E.; Rosa, E.; Stringer, M.; Castañer, R.; Revel, L. *Drug News Perspect.* **2010**, *23*, 7−36.
(96) Graul, A. I.; Cruces, E. *Drugs Today* **2011**, *47*, 27−51.
(97) Graul, A. I.; Cruces, E.; Dulsat, C.; Arias, E.; Stringer, M. *Drugs Today* **2012**, *48*, 33−77.
(98) Graul, A. I.; Lupone, B.; Cruces, E.; Stringer, M. *Drugs Today* **2013**, *49*, 33−38.
(99) Graul, A. I.; Cruces, E.; Stringer, M. *Drugs Today* **2014**, *50*, 51−100.
(100) Graul, A. I.; Navarro, D.; Dulsat, G.; Cruces, E.; Tracy, M. *Drugs Today* **2014**, *50*, 133−158.
(101) Graul, A. I.; Stringer, M. *Drugs Today* **2015**, *51*, 37−87.
(102) Newman, D. J.; Cragg, G. M.; O'Keefe, B. R. In *Modern Biopharmaceuticals, Design, Development and Optimization*; Knablein, J., Ed.; Wiley-VCH: Weinheim, 2005; Vol. *2*, pp 451−496.
(103) Boyd, M. R. In *Current Therapy in Oncology*; Neiderhuber, J., Ed.; Decker: Philadelphia, 1993; pp 11−22.
(104) Cole, W. H. *Chemotherapy of Cancer*; Lea and Febiger: Philadelphia, 1970; p 349.
(105) Sweetman, S. C. *Martindale, The Complete Drug Reference*, 33rd ed.; The Pharmaceutical Press: London, 2002.
(106) Fabbro, D.; Cowan-Jacob, S. W.; Moebitz, H. *Br. J. Pharmacol.* **2015**, *172*, 2675−2700.
(107) Fabbro, D.; Ruetz, S.; Buchdunger, E.; Cowan-Jacob, S. W.; Fendrich, G.; Liebtanz, J.; Mestan, J.; O'Reilly, T.; Traxler, P.; Chaudhuri, B.; Fretz, H.; Zimmermann, J.; Meyer, T.; Caravatti, G.; Furet, P.; Manley, P. W. *Pharmacol. Ther.* **2002**, *93*, 79−98.
(108) Vijayan, R. S. K.; He, P.; Modi, V.; Duong-Ly, K. C.; Ma, H.; Peterson, J. R.; Dunbrack, J. R. L.; Levy, R. M. *J. Med. Chem.* **2015**, *58*, 466−479.
(109) Tiligada, E.; Ishii, M.; Riccardi, C.; Spedding, M.; Simon, H.-U.; Teixeira, M. M.; Cuervo, M. L. C.; Holgate, S. T.; Levi-Schaffer, F. *Br. J. Pharmacol.* **2015**, *172*, 4217−4227.
(110) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615−4625.
(111) DeSolms, S. J.; Giuliani, E. A.; Guare, J. P.; Vacca, J. P.; Sanders, W. M.; Graham, S. L.; Wiggins, J. M.; Darke, P. L.; Sigal, I. S. *J. Med. Chem.* **1991**, *34*, 2852−2857.
(112) Ripka, A. S.; Rich, D. H. *Curr. Opin. Chem. Biol.* **1998**, *4*, 439−452.
(113) Schechter, I.; Berger, A. *Biochem. Biophys. Res. Commun.* **1967**, *27*, 157−162.
(114) Rahuel, J.; Rasetti, V.; Maibaum, J.; Rueger, H.; Goschke, R.; Cohen, N.-C.; Stutz, S.; Cumin, F.; Fuhrer, W.; Wood, J. M.; Grutter, M. G. *Chem. Biol.* **2000**, *7*, 493−504.
(115) Wood, J. M.; Maibaum, J.; Rahuel, J.; Grutter, M. G.; Cohen, N.-C.; Rasetti, V.; Ruger, H.; Goschke, R.; Stutz, S.; Fuhrer, W.; Schilling, W.; Rigollier, P.; Yamaguchi, Y.; Cumin, F.; Baum, H.-P.; Schnell, C. R.; Herold, P.; Mah, R.; Jensen, C.; O'Brien, E.; Stanton, A.; Bedigian, M. P. *Biochem. Biophys. Res. Commun.* **2003**, *308*, 698−705.

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

(116) Webb, R. L.; Schiering, N.; Sedrani, R.; Maibaum, J. *J. Med. Chem.* **2010**, *53*, 7490−7520.
(117) Politi, A.; Leonis, G.; Tzoupis, H.; Ntountaniotis, D.; Papadopoulos, M. G.; Grdadolnik, S. G.; Mavromoustakos, T. *Mol. Inf.* **2011**, *30*, 973−985.
(118) Tzoupis, H.; Leonis, G.; Megariotis, G.; Supuran, C. T.; Mavromoustakos, T.; Papadopoulos, M. G. *J. Med. Chem.* **2012**, *55*, 5784−5796.
(119) Palomo, J. M. *RSC Adv.* **2014**, *4*, 32658−32672.
(120) Over, B.; Wetzel, S.; Grutter, C.; Nakai, Y.; Renner, S.; Rauh, D.; Waldmann, H. *Nat. Chem.* **2013**, *5*, 21−28.
(121) Bauer, A.; Bronstrup, M. *Nat. Prod. Rep.* **2014**, *31*, 35−60.
(122) Kuttruff, C. A.; Eastgate, M. D.; Baran, P. S. *Nat. Prod. Rep.* **2014**, *31*, 419−432.
(123) Maier, M. E. *Org. Biomol. Chem.* **2015**, *13*, 5302−5345.
(124) Liu, Y.-Y.; Wang, Y.; Walsh, T. R.; Yi, L.-X.; Zhang, R.; Spencer, J.; Doi, Y.; Tian, G.; Dong, B.; Huang, X.; Yu, L.-F.; Gu, D.; Ren, H.; Chen, X.; Lv, L.; He, D.; Zhou, H.; Liang, Z.; Liu, J.-H.; Shen, J. *Lancet Infect. Dis.* **2015**, DOI: 10.1016/S1473-3099(15)00424-7.
(125) Hütter, R.; Keller-Schien, W.; Knüsel, F.; Prelog, V.; Rodgers, G. C., jr.; Suter, P.; Vogel, G.; Voser, W.; Zähner, H. *Helv. Chim. Acta* **1967**, *50*, 1533−1539.
(126) Kohno, J.; Kawahata, T.; Otake, T.; Morimoto, M.; Mori, H.; Ueba, N.; Nishio, M.; Kinumaki, A.; Komatsubara, S.; Kawashima, K. *Biosci., Biotechnol., Biochem.* **1996**, *60*, 1036−1037.
(127) Camp, D. *Drugs Future* **2013**, *38*, 245−256.
(128) Kantarjian, H. M.; O'Brien, S.; Cortes, J. *Clin. Lymphoma, Myeloma Leuk.* **2013**, *13*, 530−533.
(129) Maimone, T. J.; Baran, P. S. *Nat. Chem. Biol.* **2007**, *3*, 396−407.
(130) McKerrall, S. J.; Jørgensen, L.; Kuttruff, C. A.; Ungeheuer, F.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 5799−5810.
(131) Michaudel, Q.; Ishihara, Y.; Baran, P. S. *Acc. Chem. Res.* **2015**, *48*, 712−721.
(132) Shah, S.; Ryan, C. J. *Drugs Future* **2009**, *34*, 873−880.
(133) Doronina, S. O.; Mendelsohn, B. A.; Bovee, T. D.; Cerveny, C. G.; Alley, S. C.; Meyer, D. L.; Oflazoglu, E.; Toki, B. E.; Sanderson, R. J.; Zabinski, R. F.; Wahl, A. F.; Senter, P. D. *Bioconjugate Chem.* **2006**, *17*, 114−124.
(134) Smaglo, B. G.; Aldeghaither, D.; Weiner, L. M. *Nat. Rev. Clin. Oncol.* **2014**, *11*, 637−648.
(135) Tzogani, K.; Straube, M.; Hoppe, U.; Kiely, P.; O'Dea, G.; Enzmann, H.; Salmon, P.; Salmonson, T.; Pignatti, F. *J. Dermatol. Treat.* **2014**, *25*, 371−374.
(136) Teicher, B. A.; Tomaszewski, J. E. *Biochem. Pharmacol.* **2015**, *96*, 1−9.
(137) Kim, K. B.; Crews, C. M. *Nat. Prod. Rep.* **2013**, *30*, 600−604.
(138) Kuemler, I.; Mortensen, C. E.; Nielsen, D. L. *Drugs Future* **2011**, *36*, 825−832.
(139) Ansell, S. M. *Expert Opin. Invest. Drugs* **2011**, *20*, 99−105.
(140) Péan, E.; Flores, B.; Hudson, I.; Sjöberg, J.; Dunder, K.; Salmonson, T.; Gisselbrecht, C.; Laane, E.; Pignatti, F. *Oncologist* **2013**, *18*, 625−633.
(141) Yano, S.; Kazuno, H.; Sato, T.; Suzuki, N.; Emura, T.; Wierzba, K.; Yamashita, J.; Tada, Y.; Yamada, Y.; Fukushima, M.; Asao, T. *Bioorg. Med. Chem.* **2004**, *12*, 3443−3450.
(142) Lee, H. Z.; Kwitkowski, V. E.; Del Valle, P. L.; Ricci, M. S.; Saber, H.; Habtemariam, B. A.; Bullock, J.; Bloomquist, E.; Li, S. Y.; Chen, X. H.; Brown, J.; Mehrotra, N.; Dorff, S.; Charlab, R.; Kane, R. C.; Kaminskas, E.; Justice, R.; Farrell, A. T.; Pazdur, R. *Clin. Cancer Res.* **2015**, *21*, 2666−2670.
(143) Thorkildsen, C.; Neve, S.; Larsen, B. J.; Meier, E.; Petersen, J. S. *J. Pharmacol. Exp. Ther.* **2003**, *307*, 490−496.
(144) Wang, Y.; Serradell, N.; Rosa, E.; Castaner, R. *Drugs Future* **2008**, *33*, 473−477.
(145) Yoshida, T.; Akahoshi, F.; Sakashita, H.; Kitajima, H.; Nakamura, M.; Sonda, S.; Takeuchi, M.; Tanaka, Y.; Ueda, N.; Sekiguchi, S.; Ishige, T.; Shima, K.; Nabeno, M.; Abe, Y.; Anabuki, J.; Soejima, A.; Yoshida, K.; Takashina, Y.; Ishii, S.; Kiuchi, S.; Fukuda, S.; Tsutsumiuchi, R.; Kosaka, K.; Murozono, T.; Nakamaru, Y.; Utsumi, H.; Masutomi, N.; Kishida, H.; Miyaguchi, I.; Hayashi, Y. *Bioorg. Med. Chem.* **2012**, *20*, 5705−5719.
(146) Kato, N.; Oka, M.; Murase, T.; Yoshida, M.; Sakairi, M.; Yamashita, S.; Yasuda, Y.; Yoshikawa, A.; Hayashi, Y.; Makino, M.; Takeda, M.; Mirensha, Y.; Kakigami, T. *Bioorg. Med. Chem.* **2011**, *19*, 7221−7227.
(147) Cole, P.; Vicente, M.; Castañer, R. *Drugs Future* **2008**, *33*, 745−751.
(148) Chao, E. C. *Drugs Future* **2011**, *36*, 351−357.
(149) White, J. R., Jr. *Ann. Pharmacother.* **2015**, *49*, 582−598.
(150) Imamura, M.; Nakanishi, K.; Suzuki, T.; Ikegai, K.; Shiraki, R.; Ogiyama, T.; Murakami, T.; Kurosaki, E.; Noda, A.; Kobayashi, Y.; Yokota, M.; Koide, T.; Kosakai, K.; Ohkura, Y.; Takeuchi, M.; Tomiyama, H.; Ohta, M. *Bioorg. Med. Chem.* **2012**, *20*, 3263−3279.
(151) Tiwari, A. *Drugs Future* **2012**, *37*, 637−643.
(152) Poole, R. M.; Prossler, J. E. *Drugs* **2014**, *74*, 939−944.
(153) Wilson, M. C.; Mori, T.; Rückert, C.; Uria, A. R.; Helf, M. J.; Takada, K.; Gernert, C.; Steffens, U. A. E.; Heycke, N.; Schmitt, S.; Rinke, C.; Helfrich, E. J. N.; Brachmann, A. O.; Gurgui, C.; Wakimoto, T.; Kracht, M.; Crüsemann, M.; Hentschel, U.; Abe, I.; Matsunaga, S.; Kalinowski, J.; Takeyama, H.; Piel, J. *Nature* **2014**, *506*, 58−62.
(154) Schofield, M. M.; Jain, S.; Porat, D.; Dick, G. J.; Sherman, D. H. *Environ. Microbiol.* **2015**, *17*, 3964−3975.
(155) Kusari, S.; Lamshöft, M.; Kusari, P.; Gottfried, S.; Zühlke, S.; Louven, K.; Hentschel, U.; Kayser, O.; Spiteller, M. *J. Nat. Prod.* **2014**, *77*, 2577−2584.
(156) Kusari, P.; Kusari, S.; Spiteller, M.; Kayser, O. *Appl. Microbiol. Biotechnol.* **2015**, *99*, 5383−5390.
(157) El-Elimat, T.; Raja, H. A.; Graf, T. N.; Faeth, S. H.; Cech, N. B.; Oberlies, N. H. *J. Nat. Prod.* **2014**, *77*, 193−199.
(158) Wang, W.-X.; Kusari, S.; Sezgin, S.; Lamshöft, M.; Kusari, P.; Kayser, O.; Spiteller, M. *Appl. Microbiol. Biotechnol.* **2015**, *99*, 7651−7662.
(159) Luo, Y.; Enghiad, B.; Zhao, H. *Nat. Prod. Rep.* **2016**, DOI: 10.1039/C5NP00085H.
(160) Mohimani, H.; Pevzner, P. A. *Nat. Prod. Rep.* **2016**, *33*, 73−86.
(161) Winn, M.; Fyans, J. K.; Zhuo, Y.; Micklefield, J. *Nat. Prod. Rep.* **2016**, DOI: 10.1039/C5NP00099H.
(162) Zarins-Tutt, J. S.; Barberi, T. T.; Gao, H.; Mearns-Spragg, A.; Zhang, L.; Newman, D. J.; Goss, R. J. M. *Nat. Prod. Rep.* **2016**, *33*, 54−72.
(163) Martinez, J. P.; Sasse, F.; Bronstrup, M.; Diez, J.; Meyerhans, A. *Nat. Prod. Rep.* **2015**, *32*, 29−48.
(164) Harvey, A. L.; Edrada-Ebel, R.; Quinn, R. J. *Nat. Rev. Drug Discovery* **2015**, *14*, 111−129.
(165) Butler, M. S.; Robertson, A. A. B.; Cooper, M. A. *Nat. Prod. Rep.* **2014**, *31*, 1612−1661.
(166) Aeluri, M.; Chamakuri, S.; Dasari, B.; Guduru, S. K. R.; Jimmidi, R.; Jogula, S.; Arya, P. *Chem. Rev.* **2014**, *114*, 4640−4694.
(167) Milroy, L.-G.; Grossmann, T. N.; Hennig, S.; Brunsveld, L.; Ottmann, C. *Chem. Rev.* **2014**, *114*, 4695−4748.
(168) Nicolaou, K. C. *Angew. Chem., Int. Ed.* **2014**, *53*, 2−15.
(169) Liu, K. K.-C.; Sakya, S. M.; O'Donnell, C. J.; Flick, A. C.; Li, J. W.-H. *Bioorg. Med. Chem.* **2011**, *19*, 1136−1154.
(170) Liu, K. K.-C.; Sakya, S. M.; O'Donnell, C. J.; Flick, A. C.; Ding, H. X. *Bioorg. Med. Chem.* **2012**, *20*, 1155−1174.
(171) Ding, H. X.; Liu, K. K.-C.; Sakya, S. M.; Flick, A. C.; O'Donnell, C. J. *Bioorg. Med. Chem.* **2013**, *21*, 2795−2825.
(172) Ding, H. X.; Leverett, C. A.; Kyne, R. E., Jr.; Liu, K. K.-C.; Sakya, S. M.; Flick, A. C.; O'Donnell, C. J. *Bioorg. Med. Chem.* **2014**, *22*, 2005−2032.
(173) Ding, H. X.; Leverett, C. A.; Kyne, R. E., Jr.; Liu, K. K.-C.; Fink, S. J.; Flick, A. C.; O'Donnell, C. J. *Bioorg. Med. Chem.* **2015**, *23*, 1895−1922.
(174) Hay, M.; Thomas, D. W.; Craighead, J. L.; Economides, C.; Rosenthal, J. *Nat. Biotechnol.* **2014**, *32*, 40−51.
(175) Moffat, J. G.; Rudolph, J.; Bailey, D. *Nat. Rev. Drug Discovery* **2014**, *13*, 588−602.

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661

(176) Newman, D. J. *Pharmacol. Ther.* **2015**, DOI: 10.1016/j.pharmthera.2015.12.002.
(177) McKerrow, J. H. *Nat. Prod. Rep.* **2015**, *32*, 1610−1611.
(178) Wang, J.; Zhang, C.-J.; Chia, W. N.; Loh, C. C. Y.; Li, Z.; Lee, Y. M.; He, Y.; Yuan, L.-X.; Lim, T. K.; Liu, M.; Liew, C. X.; Lee, Y. Q.; Zhang, J.; Lu, N.; Lim, C. T.; Hua, Z.-C.; Liu, B.; Shen, H.-M.; Tan, K. S. W.; Lin, Q. *Nat. Commun.* **2015**, *6*, 10111.

DOI: 10.1021/acs.jnatprod.5b01055
J. Nat. Prod. 2016, 79, 629−661