This is an open access article published under an ACS AuthorChoice License, which permits copying and redistribution of the article or any adaptations for non-commercial purposes.

Journal of Medicinal Chemistry

Perspective

pubs.acs.org/jmc

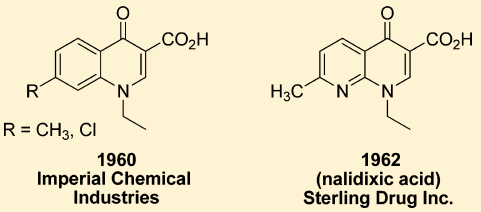
Origins of the Quinolone Class of Antibacterials: An Expanded "Discovery Story"

Miniperspective

Gregory S. Bisacchi*

AstraZeneca, 35 Gatehouse Drive, Waltham, Massachusetts 02451, United States

ABSTRACT: Published descriptions of the specific lines of research leading to the discovery of therapeutically important medicines, especially major new class medicines, have long provided value to the biopharmaceutical community as models of success, often influencing the strategies and methods of subsequent drug research. Quinolone antibacterials represent one of medicine's most important classes of anti-infective agents; yet in contrast to many other classes of anti-infectives, astonishingly few details concerning the origin of the class or the rationale leading to the selection of the first clinical agent, nalidixic acid, were ever published by the discoverers. Moreover, earlier disclosures of an independent discovery of the quinolone class of antibacterials have been almost entirely overlooked by the scientific literature. This review brings together all the available information from primary literature sources relating to both discoveries and provides for the first time a much fuller, if still partially speculative, story of the earliest years of this important class of drugs.



INTRODUCTION

The following excerpt from a 2005 review of the field of antibacterial quinolones is representative of descriptions in the scientific literature concerning the origin of the class:

> *"The first antimicrobial quinolone was discovered about 50 years ago as an impurity in the chemical manufacture of a batch of the antimalarial agent chloroquine (Figure 2). It demonstrated anti Gram-negative antibacterial activity, but its potency and antimicrobial spectrum were not significant enough to be useful in therapy. Building on this lead, however, subsequently nalidixic acid was commercialized."*[1]

"Figure 2" from that review depicts the structure of the key impurity **1**, a quinolone core compound, as well as the structure of nalidixic acid **2**, a 1,8-naphthyridone core compound (see Figure 1 in the current review). As explained in more detail below, the above excerpt surprisingly encompasses essentially all the information concerning the origin of nalidixic acid published by its discoverers at Sterling Drug (now part of Sanofi) and moreover may even be making inferences beyond the data available from Sterling's published literature (i.e., "... potency and antimicrobial spectrum [of compound **1**] were not significant enough to be useful in therapy"). For many purposes, as for inclusion in review articles and general scientific books on pharmaceuticals and anti-infectives, summaries that convey the "discovery story" in one or two sentences may be adequate. However, for scientists involved in the strategy of drug discovery wishing to know the underlying rationale and data leading to the selection of significant first-in-class drugs (in this case nalidixic acid) they are inadequate, as there are many highly pertinent questions that remain unanswered. For nalidixic acid, such questions include the following: (1) What SAR or other influences led to the switch from the quinolone core of lead compound ("impurity") **1** to the 1,8-naphthyridone core of the launched drug nalidixic acid? (2) What is the antibacterial potency and spectrum of **1**, and in what ways did nalidixic acid improve upon it? (3) What is the chemical mechanism for the formation of **1** as an impurity? Additionally, from a general context and priority point of view, the following questions require clear answers as well: (4) Was the 3-carboxy substituted quinolone or naphthyridone core a unique chemical structure at the time of Sterling's 1962

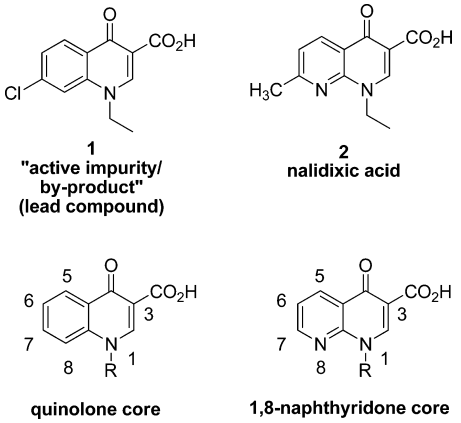


Figure 1. Structure of the chloroquine synthesis "active impurity" ("byproduct") **1** which led Sterling Drug to the identification of nalidixic acid **2**; quinolone **1** was also listed as a patent example in ICI's GB830832. Shown are the core structures and numbering of quinolones and corresponding 1,8-naphthyridones.

Received: December 4, 2014
Published: March 4, 2015

 © 2015 American Chemical Society

DOI: 10.1021/jm501881c
J. Med. Chem. 2015, 58, 4874−4882

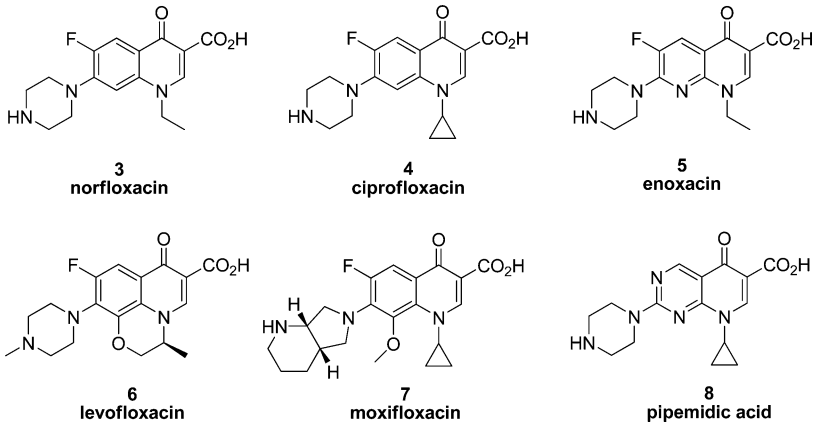


Figure 2. Structures of representative quinolones (including core variants) introduced into clinical practice over the past several decades.

disclosure of nalidixic, and if not, had antibacterial activity previously been reported with similar structures? (5) If antibacterial activity had previously been observed with such structures, what led to that independent discovery, why was that effort largely overlooked in the quinolone scientific literature, and why did launched drugs not emerge directly from those efforts? On the basis of primary literature from a number of disparate sources, this review will provide answers to most of these key questions. In some instances definitive answers are still not possible, but the author has made educated guesses pertaining to the drug discovery logic that *might* have been applied at that time which then resulted in certain events and decisions. Those instances wherein informed speculation must substitute for available facts will be clearly highlighted as such.

For the purpose of wider context, the following is a brief account of the key achievements over 5 decades in the antibacterial quinolone field after the launch of nalidixic acid. For further information on this subject the reader is directed to key reviews and books selected from a vast literature.[1−17] Both quinolone and 1,8-naphthyridone based antibacterial drugs today are often informally included within the broad, generally interchangeable designations "quinolone" or "fluoroquinolone" antibacterial class; occasionally, the 1,8-naphthyridone core is referred to as an 8-azaquinolone. In the 15 or so years following the 1964[3] clinical introduction in the United States of nalidixic acid by Sterling Drug, a number of follow-on agents were launched by other companies (Sterling itself later launched two additional drugs from this class for human use, rosoxacin and amifloxacin). At first, agents within this class occupied a fairly narrow therapeutic niche, being used primarily for treatment of urinary tract infections caused by *Escherichia coli* and a few other Gram negative pathogens. However, the therapeutic utility of the class increased dramatically starting in the early 1980s following the discovery that substitution at the quinolone (or 1,8-naphthyridone) 6-position with fluorine and at the 7-position with a basic amino heterocyclic group together greatly enhanced the antimicrobial potency and expanded the microbiological spectrum of these agents. These fluoroquinolones allowed effective treatment of infections caused by significant Gram negative pathogens such as *Pseudomonas aeruginosa*. Norfloxacin (**3**) was the first such fluoroquinolone (Figure 2). Over the following decades, pharmaceutical companies have launched agents derived from both core types (e.g., ciprofloxacin **4**, a quinolone, and enoxacin **5**, a 1,8-naphthyridone, Figure 2). There appears to be no firm consensus in the field to suggest whether the naphthyridone compared to the quinolone core offers any significant intrinsic advantages for therapy. Rather, choice of peripheral substituents dominates effects on antibacterial potency, spectrum, pharmacokinetics, and safety more than the choice of quinolone vs naphthyridone core. The quinolone core does, however, have the technical advantage of the availability of the 8-carbon as an additional site for substitution, a feature exploited in several commercially successful quinolones, among them levofloxacin **6** and moxifloxacin **7**. Although many other core variations besides quinolones and 1,8-naphthyridones have been tested, and several such variations have even been launched (e.g., pipemidic acid **8**), the quinolone and naphthyridone-based agents have remained the dominant core variations within the class. During the past 2 decades or so, launches of new agents having the quinolone core have surpassed launches of new 1,8-naphthyridone-based drugs[1,17] Over the years, the clinically useful microbiological spectrum of the quinolone class has expanded further to include many Gram positive pathogens, such as *Staphylococcus aureus*.[18−22] Although marketed quinolones have proven to have a favorable safety profile, adverse events have inevitably arisen within this class of drugs, as with most classes of drugs. As a result, a number of entrants have been withdrawn over the decades or their use restricted because of various reasons (cardiovascular issues or hepatotoxicity for example).[23−25] Moreover, therapy with quinolones is associated with an increased risk for tendinitis and tendon rupture. Nevertheless, within the field of anti-infectives, the number of clinical introductions within this class over the past 5 decades has been rivaled only by the number of introductions of all β-lactam antibacterials (penicillins, cephalosporins, and carbapenems). The quinolone class of antibacterials has been spectacularly successful from both a medical and a commercial point of view.[26] Therefore, the first-in-class introduction of nalidixic acid by Sterling must be regarded as a highly important pharmaceutical achievement, having a remarkable and long-lasting positive influence on medicine.

■ ORIGIN OF NALIDIXIC ACID: THE MYSTERY BEGINS

Considering the vast and still growing literature on (fluoro)-quinolone antibacterials and the medical and commercial importance of this class, it may seem surprising that the lines of research leading to the identification of nalidixic acid had been nearly a complete mystery to the drug discovery community for several decades following its first disclosures.

DOI: 10.1021/jm501881c
J. Med. Chem. 2015, 58, 4874−4882

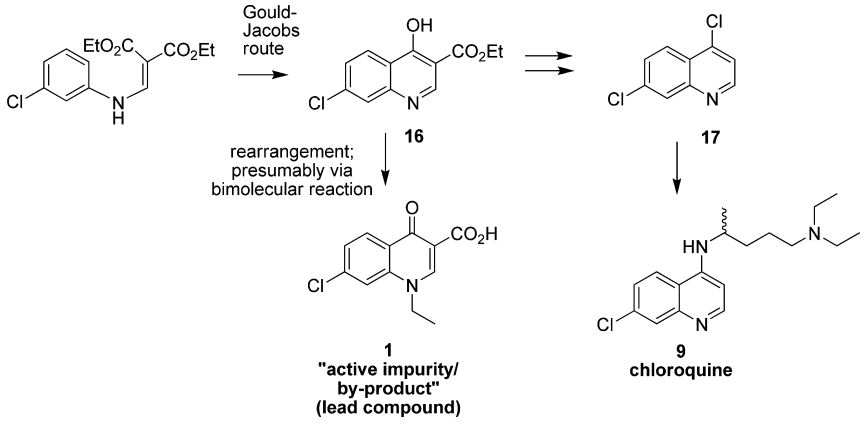


Figure 3. Synthesis of the antimalarial chloroquine (**9**) via the Gould-Jacobs route for generation of **16** and **17** and showing the formation of the key "active impurity" (**1**) which served as a lead structure for the Sterling naphthyridone program.

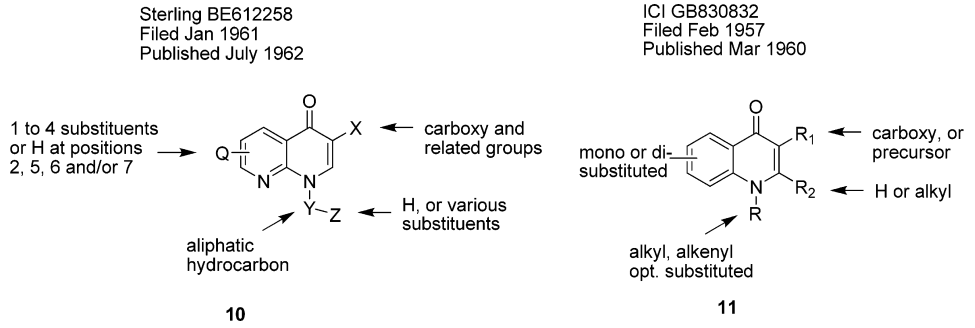


Figure 4. Markush structures **10** and **11** contained in Sterling patent BE612258 (published July 1962) and ICI patent GB830832 (published Mar 1960), respectively.

David Greenwood stated in his 2008 book "Antimicrobial Drugs: Chronicle of a Twentieth Century Medical Triumph" that "Sterling-Winthrop was reticent about revealing details of the discovery".[27]

The mystery began in the highly cited 1962 Sterling paper entitled "1,8-Naphthyridine derivatives. A new class of chemotherapeutic agents", which described the antibacterial properties of a small panel of 3-carboxy-1,8-naphthyridones and which specifically identified nalidixic acid as a promising new antibacterial agent.[28] George Lesher, the lead author and acknowledged discoverer of nalidixic acid, stated in a footnote within this paper:

> *"In vitro and in vivo antibacterial activity was found in a series of 1-alkyl-4-quinolone-3-carboxylic acid derivatives: A. R. Surrey and G. Y. Lesher et al., to be published".*[28]

That promised follow-up paper, specifically on quinolone (as opposed to 1,8-naphthyridone) core agents, was never published. Proceedings to the 1963 International Congress of Chemotherapy (Stuttgart) were published in 1964[29] and included another early disclosure by Lesher of nalidixic acid with footnotes referencing two other papers designated "to be published" having the following titles: "Antibacterial agents I. The synthesis of 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids", and "Antibacterial agents II. The synthesis of 1-alkyl-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acids".

These intended follow-up papers, the first describing a quinolone core series and the second covering a naphthyridone core series, held the promise of possibly providing some expanded context and clarifying the lines of research that led to the selection of nalidixic acid, a naphthyridone, as the optimal analog to launch for clinical use. However, no papers were ever published having those titles. Therefore, the mystery persisted regarding the details surrounding the discovery of the class at Sterling and the specific selection of nalidixic acid as a launched drug.

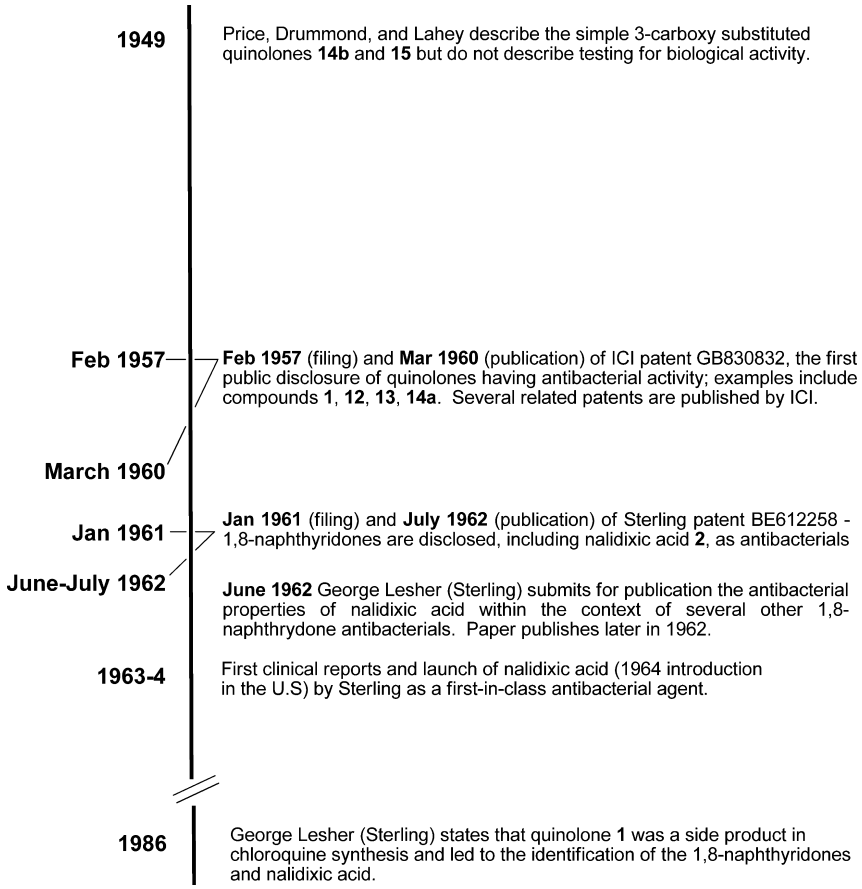
Eventually, nearly 30 years after Lesher's initial work on the class, a brief description of the events leading up to the discovery of nalidixic acid was communicated. As stated by David Greenwood: "Details of the circumstances surrounding the discovery remained unclear until 1986 when George Lesher gave an account of the events at a symposium on quinolone agents in Chicago." A Sterling scientist who had worked with George Lesher (although after the discovery of nalidixic acid) wrote a tribute to Lesher after Lesher's death in 1990 that contained the following description, taken from the 1986 symposium:[30]

> *"As part of a study at Sterling in the late 1950s aimed at the identification of by-products of the synthesis of the important antimalarial drug chloroquine, he [Lesher] and his co-workers isolated and characterized 7-chloro-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid. This by-product was a regioisomer of the normal intermediate in the process, ethyl 7-chloro-1,4-dihydro-4-oxo-3-quinolinecarboxylate. The by-product exhibited modest in vitro antibacterial properties and served as the lead structure of the design and synthesis of additional analogs. Among those new derivatives was the 1,8-naphthyridine analog nalidixic acid."*

This description, published in a book in 1993,[31] is consistent with the 1962 Lesher footnote, inasmuch as both refer to the Sterling lead structure having a quinolone (rather than naphthyridone) core, now identified specifically as 7-chloro-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (compound

DOI: 10.1021/jm501881c
J. Med. Chem. 2015, 58, 4874−4882

Chart 1. Timeline of Key Events in the Early History of Quinolone/Naphthyridone Antibacterials



1). Further, the 1986 lecture by Lesher and the 1993 written account of that lecture for the first time identified the synthesis of the antimalarial chloroquine (**9**, Figure 3) as the general source of that antibacterial quinolone lead compound. Sterling Drug was actively involved with chloroquine synthesis and manufacture during the 1940s and 1950s, so the serendipitous detection of such a byproduct would not be surprising from a drug discovery perspective. At least one other example exists of the discovery of a new class of anti-infective from a byproduct isolated during the synthesis of an unrelated class of therapeutics.[32,33]

A question that immediately arises, however, and that apparently has never been specifically addressed previously, is why Sterling decided to switch to a naphthyridone core (the core of nalidixic acid (**2**)) when the lead compound from the chloroquine synthesis was actually a quinolone core structure (**1**). The published record seems to be silent on the rationale behind this key decision at Sterling. The first patent from Sterling, BE612258, on the subject of naphthyridone antibacterials was published in July 1962 and contained the Markush structure **10** (Figure 4), specifically claiming only 1,8-naphthyridones; quinolone core structures would automatically be excluded from such a claim.[34] Subsequent Sterling patents for several years did not depict nor refer to quinolone core antibacterials even though Sterling had experience with that core series, as judged by two of the titles of the nonpublished papers referred to by Lesher in 1962 and 1964. Why did Sterling not claim (or publish) quinolone structures during those early years?

IMPERIAL CHEMICAL INDUSTRIES (ICI): FIRST TO DISCLOSE

As it happened, a series of three patents from Imperial Chemical Industries (ICI) had already been published from March to May of 1960 on the topic of quinolone core antibacterials, 2 years prior to the June 1962 date that Lesher submitted his highly cited first disclosure of nalidixic acid and also prior to the filing of any of Sterling's own naphthyridone patent applications (see timeline, Chart 1).

The pivotal ICI quinolone patent application was GB830832, filed in February of 1957 and published in March of 1960. That disclosure exemplified several dozen specific antibacterial quinolones having the key 3-carboxy substituent, among them, quinolone **1** (the Sterling "active byproduct"), **12** (the quinolone analog of nalidixic acid), **13** (a 6-fluoroquinolone), and 6-nitro analog **14a** (Figures 1 and 5).[35] This ICI patent claimed the Markush structure **11** (Figure 4), specifically covering quinolone core structures. Walter Hepworth, an ICI chemist, is listed as co-inventor on this and two of the other ICI antibacterial quinolone patents from this same time period.[36] Hepworth was also listed as sole inventor on two additional patents, published in 1959, which claimed a chemical process for the synthesis of 6-nitro-1-methyl-3-carboxyquinolone (**14b**, Figure 5).[37,38] It seems that ICI was particularly interested in antibacterial 6-nitro-3-carboxy substituted quinolones among the numerous variations described in their patents. Prior art citations listed in the two process patents indicated that ICI was aware of several 1949 papers by Australian academic researchers that had already disclosed 6-nitro substituted and 6-unsubstituted 3-carboxyquinolones **14b** and **15**, although

DOI: 10.1021/jm501881c
J. Med. Chem. 2015, 58, 4874−4882

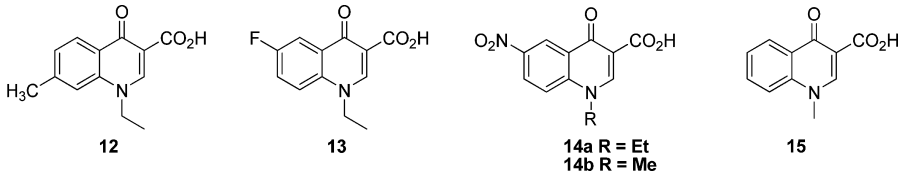


Figure 5. Structures of several examples included in ICI patent GB830832 (**12**, **13**, **14a**). Also shown are structures of compounds **14b** and **15**, disclosed in 1949 by Australian researchers.

those papers did not ascribe any biological activity to those compounds.[39−41] One might speculate that had these early simple quinolones been tested for antibacterial activity at the time of their isolation, the class of quinolone antibacterials might have emerged many years earlier (Chart 1).

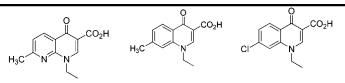
It is unknown whether George Lesher and colleagues at Sterling were aware of this extensive body of earlier ICI disclosures in the patent literature on the subject of antibacterial quinolone core structures prior to their own first filing on antibacterial naphthyridone core structures. Sterling's first naphthyridone patent was filed January 1961, 9 months following the publication of ICI's pivotal quinolone patent GB830832 and nearly 4 years after ICI filed this patent. However, one is reasonably led to presume that because of the intellectual property constraints imposed by the prior ICI patents, Sterling was ultimately compelled to file on non-quinolone (although closely related) core structures. A 1,8-naphthyridone core, which is the core of nalidixic acid, would certainly have represented one option to secure composition-of-matter claims laying outside the scope of the ICI quinolone patents.

■ STERLING: PLAYING CATCH-UP TO ICI?

Sterling must have generated early SAR of its own with quinolone (as opposed to 1,8-naphthyridone) core antibacterials, as judged by the titles of Lesher's never-published papers that were cited in the two early nalidixic acid publications of 1962 and 1964, discussed above. Two reasonable theories might now be considered to imagine how the early Sterling research could have led to 1,8-naphthyridones and nalidixic acid. The first theory proposes that following their observation of the antibacterial activity of the quinolone byproduct of chloroquine synthesis ("impurity" **1**) Sterling quickly set up a quinolone-core based SAR program; maintaining the quinolone core at least initially would be the most straightforward decision from a medicinal chemistry point of view. During the time leading up to the ICI quinolone patent publications, Sterling may well have additionally been investigating 1,8-naphthyridones as a core variation. However, if they had only quinolone-core antibacterial research, they could conceivably have spent the 9 months after ICI published GB830832 to synthesize and test a corresponding series of 1,8-naphthyridones, which then became the basis of their own first filing (BE612258). A second theory postulates that Sterling observed the antibacterial activity of the chloroquine byproduct **1** but did not immediately set up any medicinal chemistry program around it. The publication of ICI's GB830832 in March 1960 could have then motivated Sterling to initiate a traditional "fast-follow" medicinal chemistry program by first developing SAR around the quinolone-core series to provide benchmark data, followed by extending that SAR to patent-unencumbered 1,8-naphthyridone compounds. Nine months after the ICI quinolone filing published, Sterling then filed BE612258 on the napthyridone series.

Apart from intellectual property constraints at the time imposed by the prior ICI quinolone filings, there is the possibility that Sterling might have been attracted to the 1,8-naphthyridone core over the corresponding quinolone core for scientific reasons. If so, as previously noted, Sterling never published what those reasons might have been. Their own early papers described only the SAR of nalidixic acid compared to a few other closely related 1,8-naphthyridones, not against any quinolones or even against their lead compound **1**. Over the following years, however, data became available in the literature that can now be used to effectively provide "head-to-head" minimum inhibitory concentration (MIC) comparisons of nalidixic acid **2** versus the chloroquine synthesis byproduct quinolone **1** as well as versus the ICI "matched pair" nalidixic acid quinolone analog **12** (Table 1). These data, merged from

Table 1. Comparison of MIC[a] Values for Nalidixic Acid 2, ICI Compound 12 (Quinolone Core Version of Nalidixic Acid), and Chloroquine Synthesis "Byproduct" 1



	2	12	1	
	nalidixic acid; Sterling	ICI patent GB830832 example	chloroquine synthesis by-product	
Strain	MIC (μg/ml)			Reference
E. coli NIHJ	3.13	6.25	25	A[c]
E. coli NIHJ JC-2	6.25	6.25	ND[b]	B[d]
K. pneumoniae 602	6.25	25	25	A
K. pneumoniae PCI 602	6.25	6.25	ND	B
P. mirabilis GN2425	12.5	12.5	12.5	A
P. vulgaris HX 19	1.56	12.5	25	A
S. typhi T-58	6.25	12.5	ND	B
S. aureus 209P	100	200	50	A
S. aureus 209p JC-1	>50	>50	ND	B
P. aeruginosa 104	200	>200	200	A
P. aeruginosa TU-408	>50	>50	ND	B

[a]MIC = minimum inhibitory concentration. [b]ND = no data. [c]A = H. Agui et al.[57] [d]B = A. Tani et al.[78]

the publications of two laboratories, can be viewed as a partial reconstruction of the SAR that Lesher might have used early in the Sterling program as judged by the titles of his unpublished early follow-up papers. As the data in the table show, the MIC values for all three agents are quite similar against many of the pathogens tested. However, nalidixic acid does show an in vitro advantage over the two quinolone-core analogs **1** and **12** for individual strains of *E. coli*, *Proteus vulgaris*, and *Klebsiella*

DOI: 10.1021/jm501881c
J. Med. Chem. 2015, 58, 4874−4882

pneumoniae. It is not known whether similar SAR provided Sterling an additional motivation to pursue the naphthyridone nalidixic acid as a clinical candidate in the context of their perceived ICI competitors.

Sterling subsequently filed a number of other 1,8-naphthyridone antibacterial patents, as well as other patents claiming related, but non-quinolone, cores. In 1966 Sterling filed (and published in 1969) its first quinolone-core patent but narrowly restricted its scope to phenyl and phenyl-linker substitutions at the 6- and 7-quinolone positions.[42] This claimed subject matter partially overlapped with ICI's patent claims, although ICI had not exemplified analogs having that specific type of substitution.

STERLING: A "LEAN" RECORD FOR CITATION OF RELEVANT PRIOR ART

Even though Sterling disclosed "1-alkyl-4-quinolone-3-carboxylic acid derivatives" as the basis for their naphthyridone series in 1962 and then in 1986 specifically disclosed byproduct **1** and its isolation from a synthesis of chloroquine, Sterling itself surprisingly never published or referred to any details subsequently published on the chemical mechanism that might have generated their key lead compound **1**. According to the chemical literature of the 1950s and earlier, 4,7-dichloroquinoline **17** (Figure 3) was typically the late-stage intermediate used in chloroquine synthesis and was prepared by several different methods. One of these methods, the Gould-Jacobs route, is highly relevant, since it generates the quinoline **16** having a 3-carbethoxy substituent.[43,44] Other chemical routes during that time leading to **17** placed a carbethoxy group at the quinoline 2-position or did not introduce any carboxy substituent on the ring, and those intermediates would not be relevant to the generation of **1**.[45−48] In 1967 and 1970, a group in India did publish experimental details for the formation and isolation of **1** during synthesis of chloroquine using the Gould-Jacobs route.[49,50] One is strongly led to assume that the Gould-Jacobs synthesis and the proposed mechanism shown in these papers for formation of **1** (Figure 3) are in fact what Lesher had in mind when he stated that impurity **1** was the genesis for the Sterling naphthyridone program leading to nalidixic acid. However, on the basis of a search of the literature, Sterling seems never to have cited these key Indian papers, even though the chemistry was central to their own story of the origin of nalidixic acid. These Indian publications, however, cite the ICI patent GB830832 to confirm the physical characterization of **1**, since the patent was the first and only source of physical data for that key compound at that time.

Also perhaps surprising was Sterling's lack of what might be viewed as reasonable citation of the earlier ICI quinolone disclosures. None of Sterling's first (or subsequent) naphthyridone antibacterial patents cited the ICI quinolone efforts as prior art, although Sterling's first quinolone patents from 1969 and 1972 do list ICI's GB830832 among a number of other patent citations. Conceivably, patents filed during this earlier time were governed by less rigorous standards regarding broad prior art citation than we are accustomed to today. For example, early Warner Lambert antibacterial quinolone patents[51,52] (filed 1962−1964, published 1964−1967) do not cite either ICI's or Sterling's prior disclosures, yet a quinolone filing by Lilly[53] from that period does specify ICI's GB830832 as prior art (although it does not cite any work by Sterling). More puzzling, however, was the paucity of acknowledgment by Sterling of the ICI quinolone work within the journal literature. Over the 3 decades of Sterling's journal publications on naphthyridone and quinolone antibacterial compounds, including review articles and book chapters, there appeared only in 1990 an acknowledgment of a small portion of an ICI contribution, confined to a one-sentence footnote: "[impurity compound **1**] was later described in Brit. Patent 830,832 (ICI) 1960."[54] Technically, this is likely a correct statement: Sterling almost certainly discovered the initial antibacterial activity in **1** preceding the publication in 1960 by ICI of its patent which depicted **1** as a specific example. However, the language of this footnote overlooks the parallel conclusion that ICI would obviously also have discovered the antibacterial activity in quinolone structures before they published GB830332 in 1960; indeed, ICI filed the patent application in early 1957, and therefore, they could have made the discovery of **1** prior to this even earlier date. Thus, this statement by Sterling, intentionally or unintentionally, minimizes ICI's contribution in a significant parallel discovery.

Whereas Sterling could arguably be viewed as parsimonious in its acknowledgment of the prior ICI disclosures, ICI, for its part, never published its pioneering quinolone work in the scientific journal literature. As a result of these two major omissions, the ICI work has been essentially unrecognized as an major independent cocontribution to the discovery of an important class of antibacterials. Over the decades, only brief statements from a handful of researchers have noted ICI's contributions to the quinolone antibacterial class.[2,55−60]

ICI: NO RECORD OF THE ORIGIN OF ITS QUINOLONE PROGRAM AND A LOST OPPORTUNITY

Unfortunately, ICI never hinted in any published documents what investigations may have initially led them to their antibacterial quinolone series. However, ICI, like Sterling, was also heavily involved with antimalarial programs during the 1940s and 1950s, even publishing a chloroquine synthesis in 1951.[61] Therefore, we might speculate that they too could have serendipitously observed the same antibacterially active chloroquine impurity, potentially setting in motion their own independent quinolone program. As mentioned, the actual chloroquine byproduct **1** was in fact specifically exemplified in the ICI patent GB830832, although it was not referred to as a byproduct; it was rather presented as one additional example in the series of active quinolones synthesized via a general pathway. Alternatively, ICI was conducting an anticoccidial program in the 1950s involving 4-hydroxy-3-carboxyquinoline core compounds. Walter Hepworth was involved with this program, so an antibacterially active lead quinolone compound conceivably might have been derived from this line of research.[62] Attempts by this author (as an employee of AstraZeneca, a company whose legacy companies includes ICI) to obtain internally archived scientific documents (e.g., laboratory notebooks or reports) relating to the ICI quinolone effort of the late 1950s did not yield anything relevant. Those historical records may not have been retained by AstraZeneca or are now too difficult to locate.

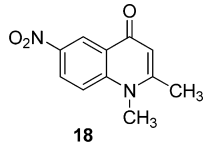
Why did ICI not pursue clinical application for any members of its groundbreaking quinolone series? A brief explanation can be found in the introduction to a 1971 paper published by Justus Landquist (the author of the 1951 ICI chloroquine synthesis publication). Landquist stated the following:

DOI: 10.1021/jm501881c
J. Med. Chem. 2015, 58, 4874−4882

> *"Some years ago, A. R. Martin discovered that certain quinolones (Ref 1) with the general formula 1 had systemic antibacterial activity. Unfortunately, the most potent of them, the 6-nitro derivatives, caused cataracts in animals of several species and the clinical use of these compounds was not possible. Following a similar observation, Lesher et al. found a clinically useful compound in the naphthyridone 2."*[63]

In this statement "Ref 1" refers to the ICI quinolone patent GB830832 and "general formula 1" is similar to the Markush structure from that patent (Figure 4) but additionally specifying a carboxy group at the 3-position; "naphthyridone 2" is nalidixic acid. 6-Nitro substituted 3-carboxyquinolones (or the corresponding naphthyridones) have not been widely represented in the antibacterial quinolone literature. Perhaps other labs subsequent to ICI's work also found such analogs to display toxicity or found them not to be sufficiently potent compared to other quinolone analogs, and thus, 6-nitro substituted quinolones were never seriously pursued as antibacterials.[64−68] It is not known specifically which 6-nitro-3-carboxyquinolones were the subject of the in vivo investigations at ICI or what level of antibacterial potency (MICs) they displayed in comparison to other analogs exemplified in the key ICI patent GB830832. Also unknown is whether ICI may have contemplated development of any of their non-nitro quinolone analogs, from which they had a fairly large selection to consider. We are therefore left to second-guess ICI's fateful decision to terminate their nascent quinolone program. Of course, decisions to terminate drug discovery and development programs have been made routinely by pharmaceutical companies since the beginning of the industry. Such decisions are typically highly individualized and are made at a particular point in time employing finite data sets and in the context of multiple competing priorities as well as management biases. In any case, judged solely by the harsh light of history, ICI did lose a significant opportunity in not further pursuing the quinolone series they independently discovered. By contrast, Sterling's choice of the modestly potent, but safe, nalidixic acid became a decision that ultimately "worked" insofar as it translated initially into an effective clinical treatment for a narrow indication (*E. coli* UTI, primarily). More significantly, it spawned a highly significant class of antibacterials widely employed therapeutically, with new entrants being added to the pipeline up to the present day.

As an addendum to the story relating to the nitro-substituted subclass of ICI's quinolone program, the following subsequent investigation is of note. In the 1970s, ICI transferred a subset of its original 1950s antibacterial quinolone collection to academic researchers who further studied some aspects of those early compounds.[69,70] Of particular interest, in addition to 3-carboxy substituted quinolones (substituted with or without 6-nitro groups), a subseries of antibacterially active 6-nitro analogs from this collection was studied that lacked the "essential" 3-carboxy group entirely. Compound **18** (Figure 6) is a representative example that ICI had patented during 1960−1961.[71,72] Preliminary data published by the academic researchers in 1980 revealed that the microbiological behavior of **18** differed from that of 3-carboxyquinolones in a number of important respects. One key difference was that while the conventional 3-carboxy quinolone **1** exerted inhibitory effects vs *E. coli* most strongly on actively growing cells, **18** showed strong cidality against bacterial cells prior to their active multiplication. These initial studies apparently have not been investigated further. From the available information, it is not clear whether these ICI 6-nitroquinolones lacking the standard 3-carboxy group might be acting by molecular mechanisms similar to those demonstrated for other clinical or preclinical classes of nitro-substituted heteroaromatic antibacterial agents (e.g., nitrofurans, nitroimidazoles, etc.) or by a novel mechanism.[73−77]



18

Figure 6. Structure of the ICI des-3-carboxy 6-nitroquinolone **18**.

CONCLUSIONS

The discovery and introduction into clinical use of entirely new and useful classes of medicine arguably represent the highest pinnacle of achievement for pharmaceutical researchers in the field. Therefore, the detailed accounts of the discoveries of new class medicines represent unique opportunities for other researchers to gain knowledge of methods, techniques, and strategies that ultimately provide a richer intellectual basis for future research and development. The author hopes that this review fills in a gap (although still incomplete in some respects) in the "discovery story" and early history of the quinolone class and, by specifically highlighting the available details of the earlier disclosed ICI discovery, balances and corrects to some extent the historical dogma of a single discoverer of this class. In this new light, for the initial discovery, both Sterling and ICI scientists should in the future be equally credited. Whether ICI's decision not to fully develop their own independent discovery of the quinolone class was a "wrong" decision could be the basis of an interesting debate. As alluded to above, any biopharmaceutical company routinely and continuously assesses the chances of ultimate success for any project versus the emerging risks of that project on a case by case basis against the demands of the larger portfolio. There is typically no black and white "right or wrong" here, and experienced scientists and managers make the best call they can under the circumstances. It is nevertheless fascinating to contemplate the parallel discoveries of Sterling and ICI and the very different outcomes based on the particular decisions of talented individuals at both companies at a similar point in history.

AUTHOR INFORMATION

Corresponding Author

*Phone: 339-222-9970. E-mail: gregory.bisacchi@astrazeneca.com.

Notes

The authors declare the following competing financial interest(s): The author is employed by AstraZeneca.

Biography

Gregory S. Bisacchi is currently Principal Scientist in Infection Chemistry at AstraZeneca, U.S., where he was involved with preclinical antibacterial drug discovery programs for 10 years. He previously was at Bristol-Myers Squibb (Princeton, NJ) and worked on infection (antibacterial, antifungal, and antiviral) and cardiovascular drug discovery programs. While at Bristol-Myers Squibb he participated in the development of the nucleoside analog entacavir, launched in 2005 as a treatment for hepatitis B virus infections. He obtained both his B.S. and Ph.D. degrees at the University of California, Los Angeles.

DOI: 10.1021/jm501881c
J. Med. Chem. 2015, 58, 4874−4882

REFERENCES

(1) Mitscher, L. A. Bacterial topoisomerase inhibitors: quinolone and pyridone antibacterial agents. *Chem. Rev.* **2005**, *105*, 559−592.
(2) Albrecht, R. Development of antibacterial agents of the nalidixic acid type. *Prog. Drug Res.* **1977**, *21*, 9−104.
(3) Lesher, G. Y. Nalidixic Acid and Other Quinolone Carboxylic Acids. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 3rd ed.; Grayson, M., Eckroth, D., Eds.; John Wiley: New York, 1978; Vol. *2*, pp 782−789.
(4) Wentland, M. P.; Cornett, J. B. Quinolone Antibacterial Agents. In *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic Press: San Diego, CA, 1985; Vol. *20*, pp 145−154.
(5) Fernandes, P. B.; Chu, D. T. W. Quinolones. In *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic Press: San Diego, CA, 1987; Vol. *22*, pp 117−126.
(6) Reuman, M.; Lesher, G. Y. Antibacterial Agents, Synthetic Quinolones. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed.; Kroschwitz, J. I., Ed.; John Wiley: New York, 1992; Vol. *2*, pp 854−869.
(7) Chu, D. T. W.; Shen, L. L. Quinolones: Synthetic Antibacterial Agents. In *Fifty Years of Antimicrobials: Past Perspectives and Future Trends*, 53rd Symposium of the Society for General Microbiology; Cambridge University Press: Cambridge, U.K., 1995; pp 111−137.
(8) Radl, S. From chloroquine to antineoplastic drugs? The story of antibacterial quinolones. *Arch. Pharm.* **1996**, *329*, 115−119.
(9) Dax, S. L. Quinolone Antibacterials. In *Antibacterial Chemotherapeutic Agents*; Dax, S. L., Ed.; Blackie Academic & Professional: London, 1997; pp 298−345.
(10) Andriole, V. T. *The Quinolones*, 3rd ed.; Academic Press: London, 2000.
(11) Scholar, E. M.; Pratt, W. B. The Fluoroquinolones. In *The Antimicrobial Drugs*, 2nd ed.; Oxford University Press: Oxford, U.K., 2000; pp 257−279.
(12) Domagala, J. M.; Hagen, S. E. Structure−Activity Relationships of the Quinolone Antibacterials in the New Millennium: Some Things Change and Some Do Not. In *Quinolone Antimicrobial Agents*, 3rd ed.; Hooper, D. C., Rubenstein, E., Eds.; ASM Press: Washington, DC, 2003; pp 3−18.
(13) Sheehan, G.; Chew, N. S. Y. The History of Quinolones. In *Fluoroquinolone Antibiotics*; Ronald, A. R., Low, D. E., Eds.; Birkhaeuser Verlag: Basel, Switzerland, 2003; pp 1−10.
(14) Bambeke, F. V.; Michot, J. -.; Eldere, J. V.; Tulkens, P. M. Quinolones in 2005: an update. *Clin. Microbiol. Infect.* **2005**, *11*, 256−280.
(15) Andriole, V. T. The quinolones: past, present, and future. *Clin. Infect. Dis.* **2005**, *41* (Suppl. 2), S113−S119.
(16) Wagman, A. S.; Wentland, M. P. Quinolone Antibacterial Agents. In *Comprehensive Medicinal Chemistry II*; Taylor, J. B., Triggle, D., Eds.; Elsevier: Amsterdam, The Netherlands, 2007; pp 567−596.
(17) Wiles, J. A.; Bradbury, B. J.; Pucci, M. J. New quinolone antibiotics: a survey of the literature from 2005 to 2010. *Expert Opin. Ther. Pat.* **2010**, *20*, 1295−1319.
(18) Eliopoulos, G. M. Activity of newer fluoroquinolones in vitro against gram-positive bacteria. *Drugs* **1999**, *58* (Suppl.2), 23−28.
(19) Butler, M. S.; Blaskovich, M. A.; Cooper, M. A. Antibiotics in the clinical pipeline in 2013. *J. Antibiot. (Tokyo)* **2013**, *66*, 571−591.
(20) de Souza Mendes, C.; de Souza Antunes, A. Pipeline of known chemical classes of antibiotics. *Antibiotics* **2013**, *2*, 500−534.
(21) Qin, X.; Huang, H. Review of nemonoxacin with special focus on clinical development. *Drug Des. Dev. Ther.* **2014**, *8*, 765−774.
(22) Odagiri, T.; Inagaki, H.; Sugimoto, Y.; Nagamochi, M.; Miyauchi, R. N.; Kuroyanagi, J.; Kitamura, T.; Komoriya, S.; Takahashi, H. Design, synthesis, and biological evaluations of novel 7-[7-amino-7-methyl-5-azaspiro[2.4]heptan-5-yl]-8-methoxyquinolines with potent antibacterial activity against respiratory pathogens. *J. Med. Chem.* **2013**, *56*, 1974−1983.
(23) Douros, A.; Grabowski, K.; Stahlmann, R. Safety issues and drug-drug interactions with commonly used quinolones. *Expert Opin. Drug Metab. Toxicol.* **2015**, *11*, 25−39.
(24) Sousa, J.; Alves, G.; Fortuna, A.; Falcao, A. Third and fourth generation fluoroquinolone antibacterials: a systematic review of safety and toxicity profiles. *Curr. Drug Saf.* **2014**, *9*, 89−105.
(25) Schuster, D.; Laggner, C.; Langer, T. Why drugs fail—a study on side effects in new chemical entities. *Curr. Pharm. Des.* **2005**, *11*, 3545−3559.
(26) Linder, J. A.; Huang, E. S.; Steinman, M. A.; Gonzales, R.; Stafford, R. S. Fluoroquinolone prescribing in the United States: 1995 to 2002. *Am. J. Med.* **2005**, *118*, 259−268.
(27) Greenwood, D. *Antimicrobial Drugs. Chronicle of a Twentieth Century Medical Triumph*; Oxford University Press: Oxford, U.K., 2008; pp 209−268.
(28) Lesher, G. Y.; Froelich, E. J.; Gurett, M. D.; Baily, J. H.; Brundage, R. P. 1,8-Naphthyridine derivatives. A new class of chemotherapeutic agents. *J. Med. Pharm. Chem.* **1962**, *91*, 1063−1065.
(29) Lesher, G. Y. Nalidixic acid, 1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylic acid. A new antibacterial agent. *Int. Congr. Chemother., Proc.* **1964**, *2*, 1367−1369.
(30) Lesher, G. Y. Presented at the International Symposium on Quinolone Antibiotics, Chicago, IL, Sept 24−26, 1986.
(31) Wentland, M. P. In Memorium: George Y. Lesher, Ph.D. 22 February 1926 - 17 March 1990. In *Quinolone Antimicrobial Agents*, 2nd ed.; Hooper, D. C., Wolfson, J. S., Eds.; American Society for Microbiology: Washington, DC, 1993; pp xiii−xiv.
(32) Petranyi, G.; Ryder, N. S.; Stuetz, A. Allylamine derivatives: new class of synthetic antifungal agents inhibiting fungal squalene epoxidase. *Science* **1984**, *224*, 1239−1241.
(33) Stuetz, A. Synthesis and structure-activity correlations within allylamine antimycotics. *Ann. N.Y. Acad. Sci.* **1988**, *544*, 46−62.
(34) Lesher, G. Y.; Gruett, M. D. 3-X-4-Oxo-1,8-naphthyridines et Leur Preparation. BE612258, July 3, 1962.
(35) Barton, N.; Crowther, A. F.; Hepworth, W.; Richardson, N. D.; Driver, G. W. New Quinolones and Therapeutic Compositions Containing Them. GB830832, March 23, 1960.
(36) (a) Hepworth, W.; Richardson, D. N. Substituted Nitroquinolones. GB831885, April 6, 1960. (b) Crowther, A. F.; Hepworth, W.; Moreley, J. S. Pharmaceutical compositions comprising quinolone derivatives. GB835474, May 18, 1960.
(37) Hepworth, W. Manufacture of 1-Methyl-6-nitro-4-quinolone-3-carboxylic Acid. GB820295, Sep 16, 1959.
(38) Hepworth, W. Manufacture of 1-Methyl-6-nitro-4-quinolone-3-carboxylic Acid. GB822586, Oct 28, 1959.
(39) Crow, W. D.; Price, J. R. Alkaloids of the Australian Rutaceae: *Melicope fareana*. V. The structure of the alkaloids. *Aust. J. Sci. Res., Ser. B* **1949**, 282−306.
(40) Drummond, L. J.; Lahey, F. N. Alkaloids of the Australian Rutaceae: *Acronychia baueri*. III. The structure of acronycine. *Aust. J. Sci. Res., Ser. B* **1949**, 631−637.
(41) Price, J. R. Alkaloids of the Australian Rutaceae: *Melicope fareana*. IV. Some reactions of 1-methyl-4-quinolone-3-carboxylic acid, a degradation product of the alkaloids. *Aust. J. Sci. Res., Ser. B* **1949**, 272−281.
(42) Lesher, G. Y. 1-Alkyl-1,4-dihydro-4-oxo-3-quinoline-carboxylic Acids and Esters; US3472850, Oct 14, 1969.
(43) Gould, R. G.; Jacobs, W. A. Synthesis of certain substituted quinolines and 5,6-benzoquinolines. *J. Am. Chem. Soc.* **1939**, *61*, 2890−2895.
(44) Price, C. C.; Roberts, R. M. The synthesis of 4-hydroxyquinolines; through ethoxymethylene malonic ester. *J. Am. Chem. Soc.* **1946**, *68*, 1204−1208.
(45) Surrey, A. R.; Hammer, H. F. Some 7-substituted 4-aminoquinoline derivatives. *J. Am. Chem. Soc.* **1946**, *68*, 113−116.
(46) Surrey, A. R.; Cutler, R. A. The preparation of 3-halo-4-dialkylaminoalkylamino-quinoline derivatives. *J. Am. Chem. Soc.* **1946**, *68*, 2570−2574.
(47) Price, C. C.; Leonard, N. J.; Reitsma, R. H. Synthesis of 4-hydroxyquinolines; a direct synthesis from beta-anilinoacrylates. *J. Am. Chem. Soc.* **1946**, *68*, 1256−1259.

DOI: 10.1021/jm501881c
J. Med. Chem. 2015, 58, 4874−4882

(48) Kenyon, R. L.; Wiesner, J. A.; Kwartler, C. E. Chloroquine manufacture. *Ind. Eng. Chem.* **1949**, *41*, 654−662.
(49) Raychaudhuri, A.; Basu, U. P. Side products in the preparation of ethyl 7-chloro-4-hydroxyquinoline-3-carboxylate from diethyl ethoxymethylenemalonate and m-chloroaniline. *J. Indian Chem. Soc.* **1970**, *47*, 25−32.
(50) Raychaudhuri, A. Side products in the preparation of ethyl 7-chloro-4-hydroxyquinoline-3-carboxylate—an intermediate for chloroquine. *Curr. Sci.* **1967**, *36*, 459.
(51) Kaminsky, D.; Meltzer, R. I. Medicament a Base de Derives d'Acide Carboxylique. FR M4148, 1967.
(52) Kaminsky, D.; Meltzer, R. I. 1-Methyl-3-carboxy-6,7-dimethoxy-4-(1*H*)-quinolone Proteus Infection Treatment. US 3,172,811, 1965.
(53) Podmore, W. D.; Bayley, L. New Quinolone Derivatives and Compositions Comprising Them. BP1070333, 1967.
(54) Wentland, M. P. Structure-activity relationships of fluoroquinolones. *Infect. Dis. Ther.* **1990**, *5* (The New Generationof Quinolones), 1−43.
(55) Albrecht, R. Investigations about the antibacterial activity of quinolonecarboxylic acids. III. Methyl 1-ethyl-4-quinolone-3-carboxylates and some 3-substituted quinolones. *Chim. Ther.* **1973**, No. Janvier−Fevrier, 45−48.
(56) Markees, D. G.; Schwab, L. S.; Vegotsky, A. Synthesis and antibacterial activity of some substituted 4-quinolone-3-carboxylic acids. *J. Med. Chem.* **1974**, *17*, 137−139.
(57) Agui, H.; Komatsu, T.; Nakagome, T. Studies on quinoline derivatives and related compounds. II. Synthesis of 5-substituted 1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid (1). *J. Heterocycl. Chem.* **1975**, *12*, 557−563.
(58) Barreau, M.; Roquet, F. Les quinolones antibacteriennes: de l'acide nalidixique a la pefloxacine. *Actual. Chem.* **1987**, No. Juin−Juillet, 197−201.
(59) Kojima, T.; Mitsuhashi, S. History of quinolone antibacterials. *Prog. Drug Res.* **1992**, *38*, 11−17.
(60) Petersen, U. Quinolone Antibiotics: The Development of Moxifloxacin. In *Analogue-Based Drug Discovery*; Fisher, J., Ganellin, C. R., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2006; pp 315−370.
(61) Landquist, J. K. Synthetic antimalarials. Part XLVI. Some 4-dialkyl-aminoalkylaminoquinoline derivatives. *J. Chem. Soc.* **1951**, 1038−1048.
(62) Nichols, W. W.; Franklin, T. J.; Gravestock, M. B.; Bring, B. G.; Ekstrom, B.; Balganesh, T. S.; Kumar, S. A.; Doig, P.; Noonan, B. History of anti-infective research at AstraZeneca. Part I: ICI/Zeneca/AstraZeneca. *SIM News* **2009**, 218−237.
(63) Landquist, J. K. Quaternary salts of pyrido(1,2-*a*)pyrimidines. *J. Chem. Soc., Perkin Trans. 1* **1971**, *15*, 2735−2738.
(64) Artico, M.; Mai, A.; Sbardella, G.; Massa, S.; Musiu, C.; Lostia, S.; Demontis, F.; La Colla, P. Nitroquinolones with broad-spectrum antimycobacterial activity in vitro. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1651−1656.
(65) Koga, H.; Itoh, A.; Murayama, S.; Suzue, S.; Irikura, T. Structure-activity relationships of antibacterial 6,7- and 7,8-disubstituted 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids. *J. Med. Chem.* **1980**, *23*, 1358−1363.
(66) Cecchetti, V.; Fravolini, A.; Lorenzini, M. C.; Tabarrini, O.; Terni, P.; Xin, T. Studies on 6-aminoquinolones: synthesis and antibacterial evaluation of 6-amino-8-methylquinolones. *J. Med. Chem.* **1996**, *39*, 436−445.
(67) Cecchetti, V.; Clementi, S.; Cruciani, G.; Fravolini, A.; Pagella, P. G.; Savino, A.; Tabarrini, O. 6-Aminoquinolones: a new class of quinolone antibacterials? *J. Med. Chem.* **1995**, *38*, 973−982.
(68) Domagala, J. M.; Hanna, L. D.; Heifetz, C. L.; Hutt, M. P.; Mich, T. F.; Sanchez, J. P.; Solomon, M. New structure-activity relationships of the quinolone antibacterials using the target enzyme. The development and application of a DNA gyrase assay. *J. Med. Chem.* **1986**, *29*, 394−404.
(69) Mahmood, F.; Mahmood, N. H. Antibacterial action of quinolones on *Escherichia coli*. IIa. Conditions required for lethality: effect of anaerobiosis, inoculum size and media composition. *Zentralbl. Bakteriol. A* **1980**, *247*, 221−228.
(70) Mahmood, F.; Mahmood, N. H.; Holms, W. H. Antibacterial action of quinolones on *Escherichia coli*. I. Structure/activity relationship. *Zentralbl. Bakteriol. A* **1980**, *246*, 329−335.
(71) Hepworth, W.; Morley, J. S.; Stacy, G. J. Nitroquinolones. GB846611, Aug 31, 1960.
(72) Birtwell, S.; Hepworth, W. Quinoline Derivatives; GB874980, Aug 16, 1961.
(73) McOsker, C. C.; Fitzpatrick, P. M. Nitrofurantoin: mechanism of action and implications for resistance development in common uropathogens. *J. Antimicrob. Chemother.* **1994**, *33* (Suppl. A), 23−30.
(74) Edwards, D. I. Nitroimidazole drugs—action and resistance mechanisms. I. Mechanisms of action. *J. Antimicrob. Chemother.* **1993**, *31*, 9−20.
(75) Gurumurthy, M.; Mukherjee, T.; Dowd, C. S.; Singh, R.; Niyomrattanakit, P.; Tay, J. A.; Nayyar, A.; Lee, Y. S.; Cherian, J.; Boshoff, H. I.; Dick, T.; Barry, C. E., III; Manjunatha, U. H. Substrate specificity of the deazaflavin-dependent nitroreductase from *Mycobacterium tuberculosis* responsible for the bioreductive activation of bicyclic nitroimidazoles. *FEBS J.* **2012**, *279*, 113−125.
(76) Hartkoorn, R. C.; Ryabova, O. B.; Chiarelli, L. R.; Riccardi, G.; Makarov, V.; Cole, S. T. Mechanism of action of 5-nitrothiophenes against *Mycobacterium tuberculosis*. *Antimicrob. Agents Chemother.* **2014**, *58*, 2944−2947.
(77) Tiwari, R.; Moraski, G. C.; Krchnak, V.; Miller, P. A.; Colon-Martinez, M.; Herrero, E.; Oliver, A. G.; Miller, M. J. Thiolates chemically induce redox activation of BTZ043 and related potent nitroaromatic anti-tuberculosis agents. *J. Am. Chem. Soc.* **2013**, *135*, 3539−3549.
(78) Tani, J.; Mushika, Y.; Yamaguchi, T. Studies on biologically active halogenated compounds. III. Synthesis and antibacterial activity of 7-fluoromethyl-1,8-naphthyridine and quinoline derivatives. *Chem. Pharm. Bull. (Tokyo)* **1982**, *30*, 3517−3529.

DOI: 10.1021/jm501881c
J. Med. Chem. 2015, 58, 4874−4882