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Genişletilmiş Spektrumlu Beta-Laktamaz Enzimlerini Hedefleyen Yeni İnhibitörlerin Bibliyometrik Analizi

Bibliometric Analysis of New Inhibitors Targeting Extended Spectrum Beta-Lactamase Enzymes

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Abstract: Bacterial resistance to available antibiotics has increasingly become a critical issue, necessitating the search for novel inhibitors to combat resistant pathogens, particularly gram-negative bacteria. This bibliometric study aims to analyze the scientific literature on novel inhibitors for extended spectrum beta-lactamase (ESBL) enzymes, identifying the most prolific organizations, authors, journals, countries, and keywords within this research area. Data were retrieved from Dimensions and Scopus databases, with 503 out of 2086 papers (published between 2013 and 2023) meeting the inclusion criteria. Analysis and visualization were performed using R-studio software and VOSviewer©, focusing on article titles, publication years, countries, authors, journals, and keywords. The study found that the United States led in the number of publications (445) and citations (15,889), followed by France and China. The journal Antimicrobial Agents and Chemotherapy published the most articles (171) and received the highest citations. Indiana University Bloomington and Case Western Reserve University from the U.S. were the leading institutions. Robert Bonomo authored the most papers (23), while Karen Bush was the highest-cited author (1,955 citations). Key future research hotspots include "taniborbactam," "xeruborbactam," "enmetazobactam," "VNRX-5236," and "imipenem-relebactam." This study underscores the critical global efforts and contributions in developing novel inhibitors against ESBL enzymes. The findings highlight key authors, influential journals, and emerging research directions that can guide future studies in combating antibiotic resistance among gram-negative bacteria.

Keywords: Bacterial Resistance, Bibliometric Analysis, Extended Spectrum Beta-Lactamase, Inhibitors, Vosviewer

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Öz: Mevcut antibiyotiklere karşı bakteriyel direnç, özellikle gram-negatif bakterilerde dirençli patojenlerle mücadele için yeni inhibitörlerin bulunmasını zorunlu hale getirmiştir. Bu bibliyometrik çalışmanın amacı, genişletilmiş spektrumlu beta-laktamaz (GSBL) enzimlerine karşı geliştirilen yeni inhibitörler konusundaki bilimsel literatürü analiz etmek, bu araştırma alanındaki en üretken kuruluşları, yazarları, dergileri, ülkeleri ve anahtar kelimeleri belirlemektir. Veriler, 2013-2023 yılları arasında yayımlanan 2086 makaleden 503'ünün dahil edilme kriterlerini karşılayarak Dimensions ve Scopus veritabanlarından alınmıştır. Analiz ve görselleştirme süreçleri, makale başlıkları, yayımlanma yılları, ülkeler, yazarlar, dergiler ve anahtar kelimelere odaklanarak R-studio yazılımı ve VOSviewer© kullanılarak gerçekleştirilmiştir. Çalışma, yayın sayısı (445) ve atıf sayısı (15.889) bakımından Amerika Birleşik Devletleri'nin ilk sırada olduğunu, bunu Fransa ve Çin'in izlediğini ortaya koymuştur. Antimicrobial Agents and Chemotherapy dergisi, en fazla makale (171) yayımlayan ve en yüksek atıf alan dergi olmuştur. Amerika Birleşik Devletleri'nden Indiana University Bloomington ve Case Western Reserve University en önde gelen kurumlar olmuştur. Bonomo Robert en fazla makale (23) yazan kişi iken, Bush Karen en çok atıf (1.955) alan yazardır. Gelecekteki önemli araştırma alanları arasında "taniborbactam," "xeruborbactam," "enmetazobactam," "VNRX-5236" ve "imipenem-relebactam" yer almaktadır. Bu çalışma, GSBL enzimlerine karşı geliştirilen yenilikçi inhibitörler konusunda küresel araştırmaların önemini ve katkılarını vurgulamaktadır. Bulgular, gram-negatif bakterilerde antibiyotik direnciyle mücadelede gelecekteki çalışmalara rehberlik edebilecek önemli yazarları, etkili dergileri ve yükselen araştırma yönlerini vurgulamaktadır.

Anahtar Kelimeler: Bakteriyel Direnç, Bibliyometrik Analiz, Genişletilmiş Spektrumlu Beta-Laktamaz, İnhibitörler, Vosviewer

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Introduction

Bacterial resistance to available antibiotics has increasingly become a cause for concern, endangering global public health (1). The World Health Organization (WHO) has identified antimicrobial resistance (AMR) as one of the top ten global health threats. This threat is projected to jeopardize the future of modern medicine, with an estimated 10 million deaths annually by 2050 if the issue is not addressed, due to the rapid acceleration of antimicrobial resistance (2). As a response to this crisis, significant efforts are being made to develop novel β-lactam/β-lactamase inhibitors (BL/BLIs) (3-5).

Beta-lactamases are enzymes that hydrolyze the beta-lactam ring of beta-lactam antibiotics, such as penicillin and cephalosporins, and they are widely distributed in nature (6-9). Gram-negative bacteria, in particular, use this resistance mechanism to neutralize β-lactam antibiotics. There are numerous beta-lactamases, and the most commonly found in healthcare settings are Extended Spectrum Beta-lactamases (ESBLs), with diverse genes encoding these enzymes, which can be grouped into several families (9-11). The major types of ESBLs include TEM, SHV, and CTX-M. Infections caused by ESBL-producing organisms pose a serious treatment challenge and are responsible for hospital-acquired infections such as pneumonia and bloodstream infections (12,13). The major pathogens associated with hospital-acquired infections include *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas* aeruginosa, and other *Enterobacteriaceae* (14–17).

Currently, many efforts are underway in the search for β-lactam/β-lactamase inhibitors (BL/BLI). Research has focused on finding new inhibitors for ESBL genes due to the limited treatment options available against the growing threat of ESBL-producing gram-negative bacteria (4, 7, 15, 18). Studies reported that beta-lactamase inhibitors such as avibactam, relebactam, vaborbactam, ceftolozane-tazobactam, and ceftazidime-avibactam can be extended to ESBL-producing organisms (9, 19). These agents exhibit properties that make them promising advancements in combating antibiotic resistance mediated by ESBLs and other beta-lactamases. Unlike traditional beta-lactamase inhibitors, such as clavulanic acid, tazobactam, and sulbactam, which work by irreversibly binding to and inactivating beta-lactamases, the new beta-lactamase inhibitors bind reversibly to the enzyme's active site without being hydrolyzed in most cases (20–23).

There is a plethora of studies on new inhibitors of ESBLs, including various types of research that provide insights into novel inhibitors. These studies encompass randomized controlled clinical trials (24), non-randomized clinical trials (25, 26), observational studies such as retrospective cohorts (14), combination protocols of BL/BLI (15), comparative studies (18), in vitro and molecular docking studies, and in silico and homology modeling studies (27, 28). In an effort to review these topics, different types of reviews have been conducted, including comprehensive reviews (11, 29), systematic reviews (10, 30), and meta-analyses (31, 32). However, a systematic bibliometric analysis summarizing the research trends in this area is lacking. Hence, this study adopts a bibliometric analysis approach to visualize the linkages between authors, research papers, institutions, and countries on this topic. This, in turn, will provide information on the extent of research on new inhibitors of ESBLs and help uncover research gaps.

Therefore, this study adopts a bibliometric analysis approach to map and visualize the research landscape of novel ESBL inhibitors. To achieve this, a comprehensive bibliometric analysis was conducted using data retrieved from the Dimensions and Scopus databases, covering the years 2013-2023. The extracted data were analyzed using VOSviewer and RStudio to visualize research collaborations, keyword trends, and influential contributions in the field. The specific objectives are to: (i) examine the evolution and distribution of research output and trends on novel inhibitors of ESBLs, (ii) identify key contributors, including researchers and institutions, and (iii) highlight future research opportunities based on bibliometric insights.

Materials and Methods

Data Search

Digital searches were conducted using the Dimensions (https://app.dimensions.ai/) and Scopus (https://www.scopus.com) databases. The search terms used were 'ESBL OR ESBL enzyme OR Inhibitor OR Nacubactam OR Zidebactam OR Vaborbactam OR Taniborbactam OR Durlobactam OR Clavulanic Acid OR Sulbactam OR Tazobactam OR Avibactam OR Relebactam OR Nacubactam' in the title and abstract.

Titles, summaries, and abstracts of relevant articles were carefully reviewed for inclusion. A total of 2,086 papers were retrieved, of which 503 were selected based on relevance and suitability (Figure 1). Ethical approval was not sought, as no human or animal subjects were involved in the study.

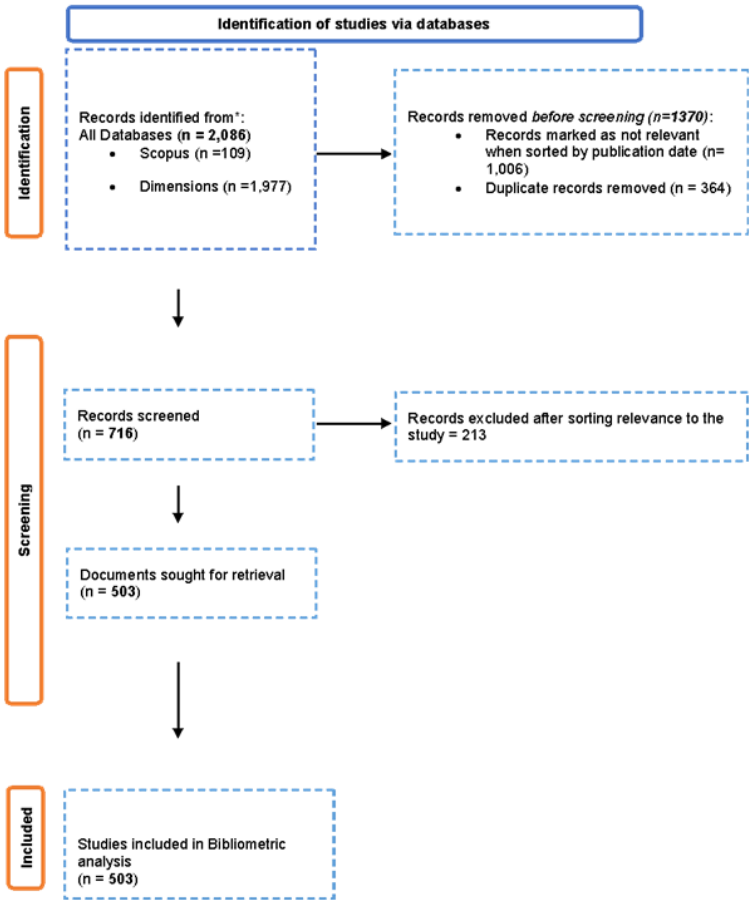

Figure 1. Database search and article selection process.

Inclusion Criteria: An article must meet the following criteria to be included: (i) It must be in English and focus on new inhibitors for the ESBL enzyme. (ii) It must be an experimental study (in vitro or in vivo). (iii) It must be a computational study (in silico, molecular docking).

Exclusion Criteria: The following types of publications were excluded: (i) Newspaper editorials, (ii) Conference proceedings, (iii) Studies published outside the study period (2013 to 2023).

Data Analysis

After document selection, data were extracted from the Dimensions and Scopus databases in XLS and CSV formats. The outcomes from the digital search were analyzed using VOSviewer (v1.6.18; Leiden University, The Netherlands) and RStudio software (v2023.03.0-daily+82.pro2). VOSviewer was employed to visually depict networks of collaborations among the analyzed variables and terms (33,34).

In the visualizations, the size of each bubble represented the quantity of publications, whereas the distance between two bubbles indicated the relatedness between terms. The color of each bubble represented the connections between different research themes (35).

Ethical Considerations of the Study

Ethical approval was not sought, as no human or animal subjects were involved in the study. The research primarily involved the collection and analysis of publicly available data from digital databases such as Dimensions and Scopus. As the study did not involve any direct interaction with human participants or animals, nor did it require the collection of personal or sensitive information, ethical review was not necessary. Additionally, all data used were non-personal, anonymized, and publicly accessible, adhering to the ethical guidelines for secondary data analysis in research.

Results

The findings of this study indicated that from 2013 to 2023, the number of articles available on new inhibitors for ESBL enzymes was significant (Figure 2). In 2021, 26 research articles were published, while in 2022 and 2023, 135 and 107 papers were published, respectively, demonstrating that the scientific community had developed a strong interest in this research topic. The highest citation count occurred in 2016, with an average citation rate of 159.

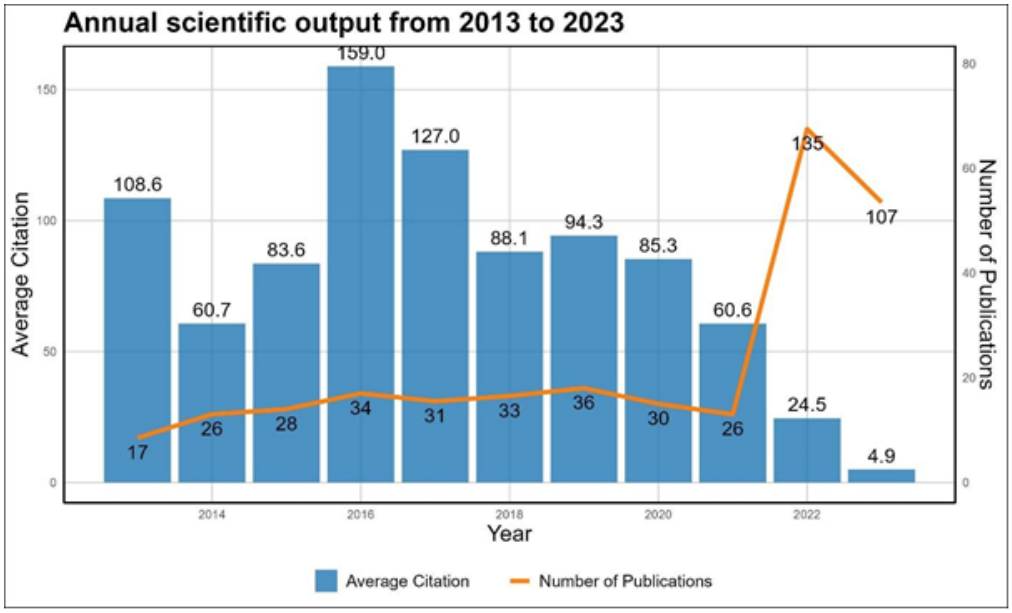

Figure 2. Publication trends and citation analysis for ESBL inhibitor research.

To provide a more detailed temporal analysis, keyword trends were examined across different years. The results indicate that in 2013-2016, the most frequently occurring keywords included "β-lactamase inhibitors," "resistance genes," and "CTX-M." From 2017 onwards, emerging terms such as "taniborbactam," "xeruborbactam," and "VNRX-5236" began to appear more frequently, highlighting the shift towards novel inhibitor research. Additionally, 2020 onwards saw an increased focus on combination therapies involving β-lactamase inhibitors, demonstrating a diversification in research approaches. Keyword co-occurrence networks illustrated that terms such as "resistance mechanisms," "novel inhibitors," and "clinical efficacy" have become more prominent in the past five years, reflecting a broader understanding of ESBL inhibitor applications.

Table 1 depicts the top countries that published the most papers related to new inhibitors for the ESBL enzyme. The United States (U.S.) led in both the number of articles (445) and citations (15,889), followed by France and China, which published 209 and 157 articles, respectively. In terms of citations, France (1,543) and China (740) garnered the most citations after the U.S. Figure 3 illustrates the collaborations

among countries involved in research on new inhibitors for the ESBL enzyme. The U.S. and France exhibited the highest level of collaboration among the countries.

Table 1. Major countries with highest publications related to inhibitors for ESBL enzyme.

Country	Documents	Citations	Total link strength
United States	445	15889	3333
France	209	5650	1543
China	157	2246	740
Japan	146	1977	625
India	137	2624	454
Spain	127	3584	1430
United Kingdom	115	2425	753
Germany	114	3259	1073
Italy	100	2816	1127
Switzerland	100	2720	764

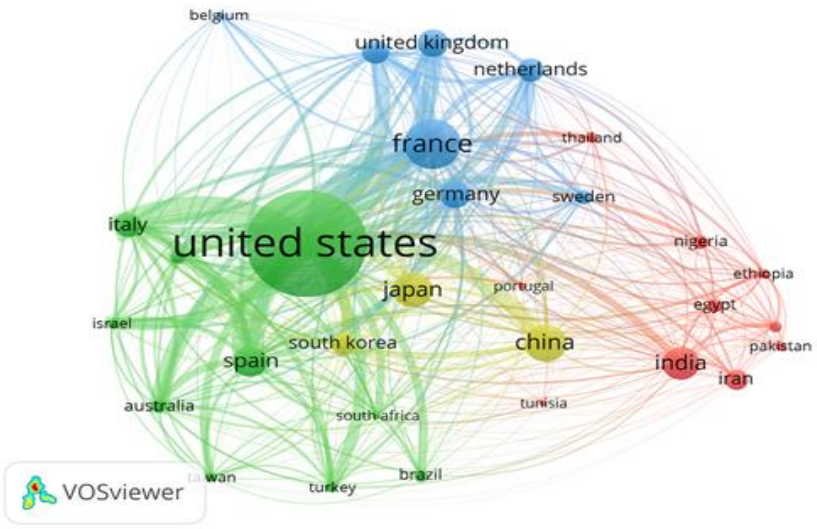

Figure 3. Network of country collaborations.

Table 2 shows the high-impact journals (sources) with the most publications in the domain of new inhibitors for the ESBL enzyme. Antimicrobial Agents and Chemotherapy and PLOS One published 171 and 86 papers, respectively, receiving 7,556 and 2,238 citations. Figure 4 illustrates the prominent journals in the field of new ESBL enzyme research.

Table 2. Top journals on new inhibitors for ESBL enzyme.

Sources	Documents	Citations	Total link strength
Antimicrobial Agents and Chemotherapy	171	7556	824
Plos One	86	2238	467
Microbial Drug Resistance	78	1069	267
International Journal of Antimicrobial Agents	68	1412	320
Journal Of Global Antimicrobial Resistance	57	692	202
Microbiology Spectrum	45	209	108
Antimicrobial Resistance & Infection Control	42	1040	298
BMC Infectious Diseases	41	948	263
Journal of Infection and Chemotherapy	38	744	123
Diagnostic Microbiology and Infectious Disease	36	521	166

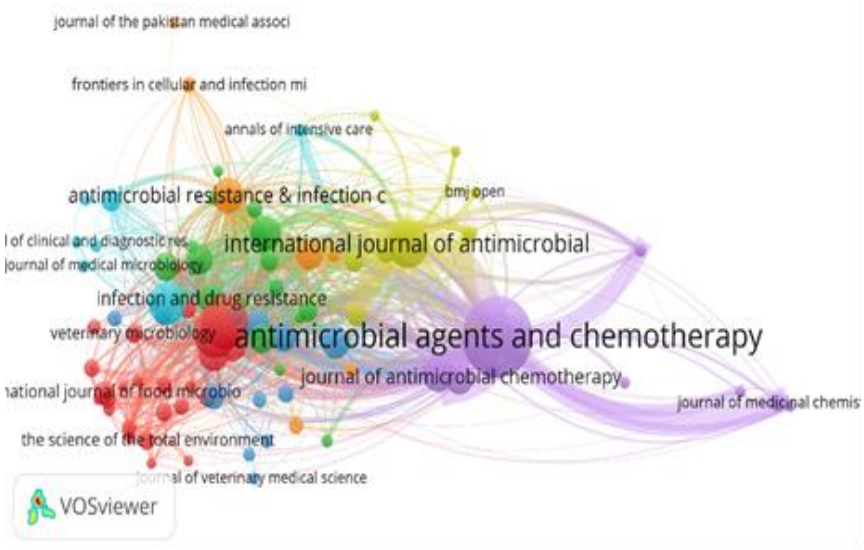

Figure 4. Lead journals on new inhibitors for ESBL enzyme.

Table 3 shows the leading organizations that published the most in the field of new inhibitors for ESBL. Indiana University Bloomington (U.S.) published 7 papers with 1,955 citations, followed by Case Western Reserve University (also from the U.S.), with 34 papers and 1,887 citations. Indiana University Bloomington received the highest number of citations.

Table 3. Top organization that published papers linked to new inhibitors for ESBL enzyme.

Organization	Documents	Citations	Total link strength
Indiana University Bloomington	7	1955	1
Case Western Reserve University	34	1887	59
Louis Stokes Cleveland Va Medical Center	23	1189	43
Utrecht University	27	1172	53
University Medical Center Utrecht	31	1169	86
Astrazeneca (United States)	18	1127	24
Hospital Universitario Virgen Macarena	17	1093	56
University Of Manitoba	15	1089	27
University Of Siena	15	1083	29
Hôpital Bichat-Claude-Bernard	18	1057	38

Table 4 indicates the top authors who published articles on new inhibitors for the ESBL enzyme. Robert Bonomo published 23 papers, followed by Mariana Castanheira, who published 20 articles. The most-cited author was Karen Bush, with 1,955 citations, followed by Robert Bonomo with 1,518 citations, and Paul-Louis Woerther with 1,120 citations.

Table 4. Top authors in research on new inhibitors for ESBL enzymes.

Author (Institution)	Documents	Citations	Total link strength
Bush, Karen	7	1955	2
Bonomo, Robert	23	1518	44
Woerther, Paul-Louis	8	1120	13
Karlowsky, James A.	7	1054	19
Hoban, Daryl J.	8	949	19
Lomovskaya, Olga	14	931	49
Andremont, Antoine	9	917	14
Castanheira, Mariana	20	845	56
Dudley, Michael N.	5	722	23
Rodríguez-Baño, Jesús	6	697	0

Table 5 presents the most highly cited original papers on new inhibitors for the ESBL enzyme. Among these, a paper by Kaushik et al., published in 2019, received the highest number of citations (36). The next most highly cited article was authored by Docobo-Pérez et al., published in 2013, which received 53 citations, followed by the work of Levasseur et al., published in 2015, with 49 citations (37, 38).

Table 5. Highly cited original articles on new inhibitors for ESBL enzyme.

Publication (DOI)	Times cited[1]	Recent citations[2]	RCR[3]	FCR[4]
10.1128/AAC.02623-18	59	25	3.19	11.92
10.1128/AAC.02190-12	53	13	1.97	7.8
10.1128/AAC.04218-14	49	7	2.18	7.99
0.1128/AAC.00164-17	47	10	2.28	9
10.1128/AAC.02596-17	42	11	2.5	7.72
0.1128/AAC.04920-14	36	13	1.66	3.31
10.1093/jac/dku237	30	5	1.36	4.74
0.1128/AAC.00757-20	30	19	2.42	7.14
10.1093/cid/ciw743	30	7	1.3	5.48

[1]Number of citations (references from other publications in Dimensions), [2]Number of citations within the past two years, [3]Relative Citation Ratio, [4]Field Citation Ratio.

Similarly, Table 6 shows the most highly influential papers on new inhibitors for the ESBL enzyme. An article by Rodríguez-Baño et al., published in 2016, garnered the highest number of citations (531) (8). Other highly cited articles include one by van Duin et al., also published in 2016, which received 449 citations (36), and a paper by Zhanel et al., published in 2013, which received 365 citations (39, 40) (Table 6).

Table 6. Highly influential papers on new inhibitors for the ESBL enzyme.

Publication (DOI)	Times cited[1]	Recent citations[2]	RCR[3]	FCR[4]
10.1128/CMR.00079-17	531	201	30.62	114.63
10.1093/cid/ciw243	449	142	21.54	82.72
10.1007/s40265-013-0013-7	365	75	12.88	37.55
10.1038/s41579-019-0159-8	340	151	20.66	45.75
10.1007/s40265-017-0851-9	300	111	17.54	40.77
10.1128/CMR.00115-20	291	235	23.42	78.6
10.1128/AAC.01443-17	266	83	13.43	43.49
10.1101/cshperspect.a025239	205	76	8.64	37.44
10.1021/acs.jmedchem.9b01518	192	104	14.89	48.04
10.1007/s10156-013-0640-7	191	34	6.92	40.95

[1]Number of citations (references from other publications in Dimensions), [2]Number of citations within the past two years, [3]Relative Citation Ratio, [4]Field Citation Ratio.

Many keywords (Figure 5a) have been used in the field of inhibitors for the ESBL enzyme. The dominant keywords identified in the current analysis, based on their frequency of occurrence, were patients (2,492), blaCTX-M (836), treatment (788), ESBL (727), carbapenem (646), and tazobactam (477). In terms of research direction, works related to new inhibitors for ESBL enzymes can be divided into three groups based on the results of keyword clusters: (1) Clinical and Epidemiological Aspects of ESBL Infections, (2) Therapeutic Strategies and Biochemical Mechanisms, and (3) Genetic and Molecular Epidemiology of ESBL Resistance (Figure 5A).

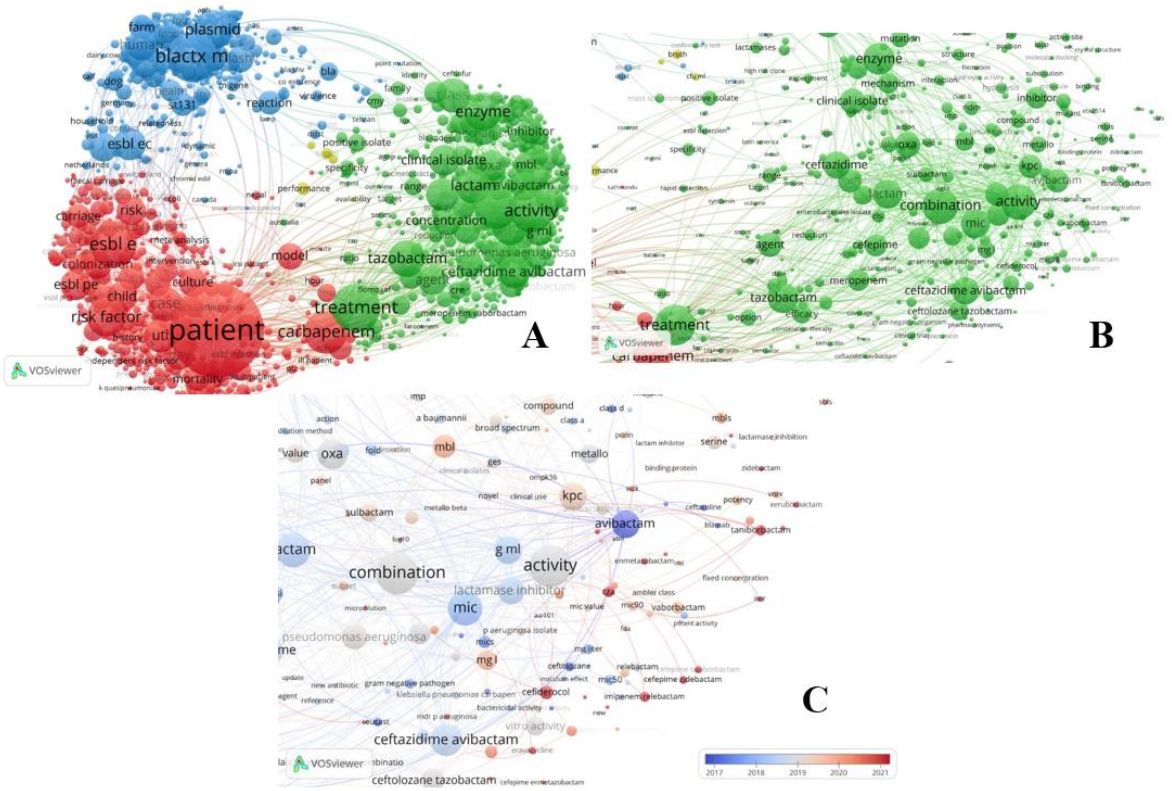

Figure 5. The co-occurrence network of the top keywords in new inhibitors for ESBL enzyme, 2013–2023

Clinical and Epidemiological Aspects of ESBL Infections (red circle): Frequently used keywords included "patients," "risk factors," "ESBL," "mortality," "colonization," "carbapenem," "transmission," "intervention," "carriage," and "UTI."

Therapeutic Strategies and Biochemical Mechanisms (green circle): Frequently used keywords included "treatment," "concentration," "activity," "meropenem-vaborbactam," "combination," "molecular docking," "potency," "ceftazidime," "avibactam," "ceftolozane-tazobactam," "vaborbactam," "taniborbactam," and "zidebactam" (Figure 5A, B).

Genetic and Molecular Epidemiology of ESBL Resistance (blue circle): Frequently used keywords included "plasmid," "blaCTX-M," "ESBL-EC," "ST131," "m gene," "blaSHV," "pair," "water," "mcr," "virulence," and "co-existence."

Different keywords were assessed over time to create a distribution map of research priorities. Figure 5C shows that "taniborbactam," "xeruborbactam," "enmetazobactam," "VNRX-5236," and "imipenem-relebactam" are emerging research hubs in the field of new inhibitors for the ESBL enzyme (Figure 5C).

Discussion

To the best of our knowledge, this bibliometric analysis is the first to focus on new inhibitors for ESBL enzymes published from 2013 to 2023. Various factors, such as leading organizations, countries, journals, keywords, and contributions by authors, have been analyzed using science mapping (40). Scientometric analysis aids in better visualizing the evolving aspects of scientific fields, enhancing understanding of a specific scientific domain, and providing forecasts about hotspots and future trends (41, 42).

A rise in the number of research outputs was observed from 2021 to 2023, likely as scientists recognized the need for newer inhibitors for the ESBL enzyme as a crucial factor in improving the fight against bacterial resistance (43). The analysis showed that the U.S., France, and China led this field, with the U.S. emerging as the leader in both paper quantity and citations. This trend has been documented earlier by several studies in similar and other scientific disciplines, such as dental medicine, regenerative endodontics, endodontics, and dental implants (44–46). The ample funding, along with substantial

scientific communities in these countries, enables researchers to carry out groundbreaking research, leading to highly impactful papers (47).

Indiana University Bloomington and Case Western Reserve University from the United States were the most prolific organizations, publishing the highest number of papers. This aligns with earlier published works, where universities from the U.S. consistently produced the most papers (33, 48). Interestingly, Karen Bush and Robert Bonomo, who were once affiliated with the Indiana University Bloomington and Case Western Reserve University, were among the most highly cited authors, making them top-rated in this domain. This highlights the Indiana University Bloomington and Case Western Reserve University as a leading organizations in this field.

A fascinating discovery in this analysis was that the majority of the publications were found in leading journals with high impact factors, underscoring the fact that publications in these journals tend to receive high citations (41). In this analysis, the journals Antimicrobial Agents and Chemotherapy and PLOS One had the highest records in terms of both publication and citations. Additionally, collaborative papers among different nations tended to have higher citation counts, further emphasizing the importance of international research efforts in this field (49).

Concerning the top-cited original paper by Kaushik et al. (36), the authors examined the antibacterial activity of novel β-lactamase inhibitors, such as relebactam and vaborbactam, in combination with β-lactams against *Mycobacterium abscessus complex* (MABC) clinical isolates through an in vitro study. They demonstrated that these agents, vaborbactam and relebactam, have significant potential as β-lactamase inhibitors and could enhance the anti-MABC activity of many carbapenems and cephalosporins, thereby improving the clinical application of these agents. The authors further recommended that additional studies should investigate the efficacy of vaborbactam and relebactam through preclinical testing and subsequent clinical trials.

The second most highly cited paper was by Docobo-Pérez et al. (37), which examined the inoculum effect on the efficacy of three agents—amoxicillin-clavulanate, piperacillin-tazobactam, and imipenem—against *E. coli* isolates recovered from an experimental murine sepsis model. These isolates included both ESBL-producing and non-ESBL-producing strains. The study's results supported the hypothesis that the inoculum effect might be responsible for the clinical failures of piperacillin-tazobactam, despite its good in vitro activity against ESBL-producing Enterobacteriaceae at high bacterial concentrations. The study also suggested that amoxicillin-clavulanate could be a second drug of choice to imipenem in treating infections caused by ESBL- and non-ESBL-producing *E. coli* strains in patients when piperacillin-tazobactam is not effective. The authors proposed that clinical studies should be designed to validate their findings in clinical applications.

Rodríguez-Baño et al. (8), in their highly cited publication, highlighted treatment options for infections caused by ESBL, AmpC, and carbapenemase-producing Enterobacteriaceae. The study discussed that drug combination therapies yielded better outcomes for high-risk patients and noted that ceftazidime-avibactam was active against KPC and OXA-48 producers. It also explored newer drugs that are active against some Carbapenemase producing-Enterobacteriaceae (CPE) and are in various stages of drug discovery and development, including agents such as meropenem-vaborbactam, imipenem-relebactam, plazomicin, cefiderocol, eravacycline, and aztreonam-avibactam. The study concluded by recommending that therapy for MDR-E infections must be individualized based on the susceptibility profile, type, and severity of the infection, as well as host factors.

Many authors have studied the role of new inhibitors for ESBL enzymes. Among the highly cited papers in our analysis, Bush and Bradford reviewed the connections between β-lactamases and new β-lactamase inhibitors (3). They studied approved inhibitor combinations, including avibactam and vaborbactam, which belong to the diazabicyclooctane and boronic acid inhibitor classes, respectively. These inhibitors were identified as promising candidates for future inhibitor design. Another study by van Duin and Bonomo highlighted the characteristics of second-generation β-lactam/β-lactamase inhibitor combinations, specifically ceftazidime/avibactam and ceftolozane/tazobactam, focusing on their

respective antimicrobial coverage and available clinical trial data (50). The study concluded that antimicrobial stewardship is crucial to preserve the activity of these agents and that pre-existing in vitro resistance should be carefully considered before their introduction into hospital formularies.

Keywords help researchers and readers easily find relevant studies. When conducting literature searches, keywords assist in reaching the intended audience by accurately reflecting the core themes of a research domain (51). In the current analysis, "taniborbactam," "xeruborbactam," "enmetazobactam," "VNRX-5236," and "imipenem-relebactam" have been identified as emerging research hotspots.

Regarding the limitations of the current analysis, bibliometric analysis uses quantitative methods; therefore, the quality of the publications was not evaluated (40). We only selected the Dimensions and Scopus databases, and articles not written in English were excluded, which may introduce selection bias. Furthermore, the data extraction process was performed manually. Despite careful checks of the databases, some errors may still persist, and readers should interpret the results of this analysis with caution.

Conclusion

A rise in annual scientific output in recent years has been observed to significantly influence the citation count of each paper. Among the countries focusing on research related to new inhibitors for ESBL enzymes, the U.S. produced the most papers and received the highest number of citations. Indiana University Bloomington and Case Western Reserve University stood out among all institutions. The majority of the articles were published in Antimicrobial Agents and Chemotherapy, which also received the highest number of citations. Among the authors, Karen Bush garnered the most citations, while Robert Bonomo published the most papers. The most cited paper was authored by Rodríguez-Baño et al. and published in Clinical Microbiology Reviews. This bibliometric analysis serves as a valuable tool for researchers, clinicians, and pharmaceutical developers to identify emerging trends, key collaborations, and potential drug candidates. The growing research interest in β-lactam/β-lactamase inhibitor combinations highlights the need for enhanced treatment strategies to address antimicrobial resistance effectively. By emphasizing the importance of continued surveillance, early resistance detection, and interdisciplinary research, this study contributes to shaping the future direction of ESBL inhibitor development and its application in clinical settings.

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It has been declared that scientific and ethical principles and the research principles in the Declaration of Helsinki were complied with during the preparation of this study, and all studies used are included in the bibliography.
Authors Contributions: Manuscript concept/design: ANA, AM – Data collecting: ANA – Data analysis/review: ANA, AM, SS – Writing the manuscript: AM, SS – Critical review of content: TGT – Final approval and responsibility: ANA, AM, SS, TGT – Material and technical support: SS, TGT – Supervision: TGT.
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