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ORIGINAL RESEARCH

Bibliometrics Analysis and Knowledge Mapping of Fragment-Based Drug Design Research: Trends from 2015 to 2024

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Purpose: This study systematically analyzed available literature related to fragment-based drug design (FBDD) published between 2015 and 2024 using bibliometric methods to identify research trends, hotspots, and emerging frontiers. The findings provide valuable information and a comprehensive reference for future FBDD research and drug development.

Methods: The relevant literature was comprehensively searched from the Web of Science Core Collection (WOSCC) database using the keywords "Fragment-based drug design" or "FBDD", covering articles published between January 1, 2015 and November 1, 2024. A total of 1,301 papers were included. Bibliometric analysis and knowledge mapping were conducted using the RStudio's bibliometrix-biblioshiny package, CiteSpace, and VOSviewer software, assessing multiple dimensions such as journal co-occurrence, keyword density, institutional collaboration, and citation patterns.

Results: The research output in FBDD revealed fluctuating growth, with an average annual growth rate of 1.42%. The United States and China lead global research with 889 and 719 publications, respectively, contributing significantly to international collaboration (34.82%). Prominent research institutions included the Center National de la Recherche Scientifique (CNRS), the University of Cambridge, and the Chinese Academy of Sciences, demonstrating strong academic influence. Key contributors such as Abell, C. Blundell, TL, and Johnson, CN, were among the top ten high-impact authors, significantly shaping the FBDD landscape through highly cited publications. Influential journals included the *Journal of Medicinal Chemistry, Journal of Chemical Information and Modeling*, and the *European Journal of Medicinal Chemistry*, each highly recognized within the FBDD research community. Keyword analysis indicated core research directions focused on "fragment-based drug discovery", "molecular docking", and "drug discovery", reflecting key technological advancements and research hotspots.

Conclusion: FBDD remains a dynamic field with ongoing global academic attention. Future research directions are likely to emphasize innovations in computational simulation, targeted drug screening, and molecular docking techniques, facilitating the advancement and development of novel therapeutic agents.

Keywords: fragment-based drug design, bibliometrics, knowledge mapping, research trends, drug discovery

Introduction

Fragment-based drug design (FBDD) is a widely adopted and promising strategy in early-stage drug discovery.[1] It involves the screening of low molecular weight compounds—known as fragments—that bind weakly to target proteins but offer high ligand efficiency and significant potential for optimization into potent drug candidates.[2,3] Since Jencks first introduced the concept in 1981, FBDD has evolved into a powerful approach that is now extensively applied by pharmaceutical companies, biotech firms, and academic research institutions.[4,5] The development of the structure-activity relationship (SAR) by nuclear magnetic resonance (NMR) approach by Shuker et al in the 1990s was a key milestone in the evolution of FBDD.[6] This technique utilized NMR spectroscopy to detect fragment binding events and

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guide their optimization into high-affinity ligands.[7] This innovation laid the foundation for the modern FBDD workflow, which typically includes fragment library design, fragment screening, structural characterization of binding interactions, and medicinal chemistry-based optimization.[8]

Advancements in biophysical screening technologies have greatly facilitated fragment identification and validation.[9,10] Common techniques include X-ray crystallography, which provides high-resolution structural information of protein–fragment complexes, although it does not directly indicate binding specificity;[11] protein-observed NMR spectroscopy, which is sensitive to binding-induced chemical shift changes but requires proteins with sufficient stability, solubility, and molecular weight compatibility;[12] and surface plasmon resonance (SPR), which offers real-time kinetic and affinity measurements, though it is limited by the requirement for target immobilization and may not be suitable for all target classes.[13] Additional methods such as thermal shift assays (TSA), microscale thermophoresis (MST), and isothermal titration calorimetry (ITC) further support fragment hit validation and ranking.[14] Compared with high-throughput screening (HTS), FBDD offers several distinct advantages. Fragment libraries are typically smaller in size (1,000–2,000 compounds), but are designed to maximize chemical diversity and ligand efficiency.[15,16] Because fragments occupy less chemical space, fewer compounds are required to sample a broad range of interactions. Moreover, fragments often possess favorable physicochemical properties such as good aqueous solubility and synthetic tractability, which are critical for downstream optimization.[17] Due to their inherently weak binding affinities (in the micromolar to millimolar range), fragments are generally screened at higher concentrations, further necessitating good solubility and stability.[18]

Once fragment hits are identified, the transition from fragment to lead compound becomes the central challenge in FBDD.[19] This process is typically achieved via three key strategies: fragment growing, fragment linking, and fragment merging.[20] Fragment growing involves the stepwise addition of substituents to a bound fragment to increase its affinity and specificity.[21] Fragment linking connects two fragments that bind to adjacent pockets within the target site, whereas fragment merging combines overlapping features of multiple fragments into a single, more potent scaffold. Each strategy requires detailed structural insights to preserve favorable interactions and avoid steric clashes or loss of binding efficiency.[22]

FBDD has contributed significantly to modern drug development, leading to the approval of eight FDA-approved drugs to date.[23] These include the BRAF inhibitor vemurafenib (2011), the CSF-1R inhibitor pexidartinib (2015), the Bcl-2 inhibitor venetoclax (2016), the FGFR inhibitor erdafitinib (2019), the serine protease inhibitor berotralstat (2020), the KRAS-G12C inhibitor sotorasib (2021), the allosteric BCR-ABL1 inhibitor asciminib (2021) and the AKT kinase inhibitor capivasertib (2023). Notably, although the majority of these drugs target kinases, the success of venetoclax and sotorasib demonstrates the potential of FBDD to tackle previously "undruggable" or protein–protein interaction targets.[24,25] In addition to approved drugs, more than 50 FBDD-derived compounds have advanced into clinical development, highlighting the broad applicability and translational impact of this approach.[26]

Despite the rapid development of FBDD, a comprehensive, systematic and quantitative evaluation of the field is still lacking. Therefore, a bibliometric analysis can provide a macroscopic overview and forward-looking insights into its development. Bibliometrics, as a subfield of library and information science, systematically measures the patterns and impacts of academic publications through detailed citation analysis.[27] This study conducted a bibliometric analysis of publications related to FBDD published from January 1, 2015 to November 1, 2024. The current research status in this field was systematically investigated through network visualization mapping, which comprehensively revealed the academic landscape and the development trends of FBDD. This analysis not only allows the impact of current research to be assessed but also provides predictive insight into the direction of development of a specific scientific field, which provides a valuable reference for future research on FBDD.

Materials and Methods

Data Acquisition

A literature search was conducted for documents published in the Web of Science Core Collection (WOSCC) (https://webofscience.clarivate.cn/wos/woscc/basic-search) between January 1, 2015 and November 1, 2024. We used keywords "Fragment-based drug design" or "FBDD" as subject terms and limited the type of document to articles. The retrieved

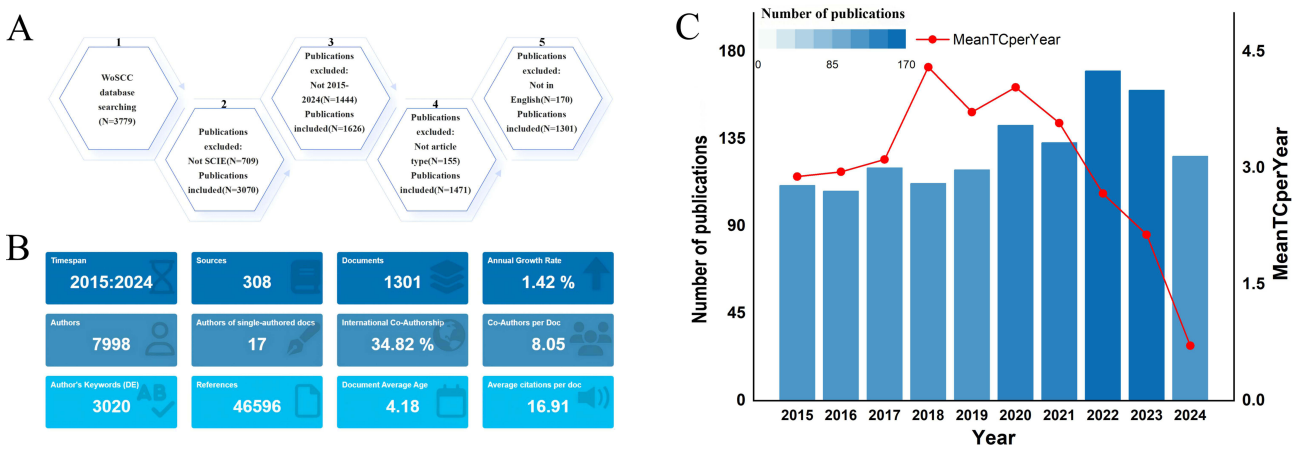

Figure 1 Methodology for data retrieval and comprehensive analysis of FBDD research. (**A**) Flowchart of the article selection process. (**B**) Overview of the 1,301 included FBDD publications. (**C**) Annual publication count and average total citations per year in FBDD research (2015–2024).

documents were exported in plain text format with complete records and citation information. The data collection and extraction processes are shown in Figure 1A.

Visualization and Data Analysis

To identify research hotspots and FBDD development trends, the data collected were exported to Microsoft Excel 2019, VOSviewer (v.1.6.20),[28] CiteSpace (v. 6.2.R7),[29] and the Bibliometrix software package (v.4.3.0, running on R 4.3.3) for further analysis.[30] The data required to generate the graphs were extracted and processed using Microsoft Excel 2019 and R 4.3.3. Journal co-occurrence and keyword density maps were generated using VOSviewer, and institution co-occurrence, keyword cluster, and reference burst maps were generated using CiteSpace.

Results

Summary of the Literature Selection

After selecting the type of paper, publication time, and language, 1,301 papers were selected for in-depth analysis in this study. Figure 1B, generated using Bibliometrix v.4.3.0, revealed the current state of FBDD research. Our analysis covered 308 journals from 2015 to 2024, with a total of 1,301 articles, an average annual publication growth rate of 1.42%. The dataset contains 7,998 authors, of which 17 articles were written by a single author, and 34.82% of the authors had international collaborations. The average number of authors per article is approximately 8–9. This study identified a total of 3,020 author keywords and 46,596 references. The life cycle of a paper (from widespread recognition to gradual lack of attention) was approximately 4.18 years, and the average number of citations per article was 16–17.

Overall Trend in the Number of Publications and Citations

The meanTCperYear is an indicator that assesses the impact of publications, calculated by dividing the number of total citations (TC) of a paper by the number of years since publication. For example, a paper that has been cited 50 times in ten years has a meanTCperYear of 5. According to Figure 1C, between 2015 and 2024, a total of 1,301 articles were published in related research, with an average of 3.011 citations per year. The highest average number of citations per article appeared in 2018, whereas the lowest value dropped to 0.71 in 2024. In terms of the number of publications, there was a slight decrease from 2015 to 2016, followed by small fluctuations in 2017 and 2018, and a peak of 142 in 2020. From 2021 onward, despite an increase in the number of publications, the average number of citations per year decreased significantly, especially in 2023 and 2024, falling to 2.14 and 0.71, respectively. This may reflect changes in research areas or a decline in interest in past research results. Therefore, researchers should focus on improving the quality and impact of their research to counteract this trend.

From 2015 to 2024, the number of publications involving FBDD showed a general trend of fluctuating growth. From 2015 to 2018, publication counts remained stable (108–120), followed by an increase in 2019 and a peak of 170 in 2022. A decline was observed in 2023 (160) and in 2024 (126). Fluctuations from 2020 to 2023 may have been influenced by the COVID-19 pandemic, which likely affected research priorities and publication patterns.

National Research Landscape: National Research Productivity and Global Collaborations

Countries were ranked based on the number of publications and the top ten countries/regions with the most publications were identified (Figure 2A). The United States ranked first with 889 publications, followed by China (719), and the United Kingdom (404). Of these top ten countries, five are located in Europe, two in North America, one in Asia, and one in Oceania. According to Figure 2B, the annual number of publications in this field in the United States, China, the United Kingdom, Germany, and Japan fluctuated between 2015 and 2024. The United States consistently led the classification in all years, reflecting its significant research output and academic influence. The number of publications from China has continued to increase since 2016, with a particularly significant increase after 2020, indicating its increasing research activity in this field. The UK ranked third in terms of publication volume, with a relatively stable overall trend, but was more active in 2020 and 2023. In contrast, the research output of Germany was relatively stable, and Japan had the lowest number of publications among the five countries but continued to participate in research activities. Overall, the United States and China were the main research forces in this field during the study period.

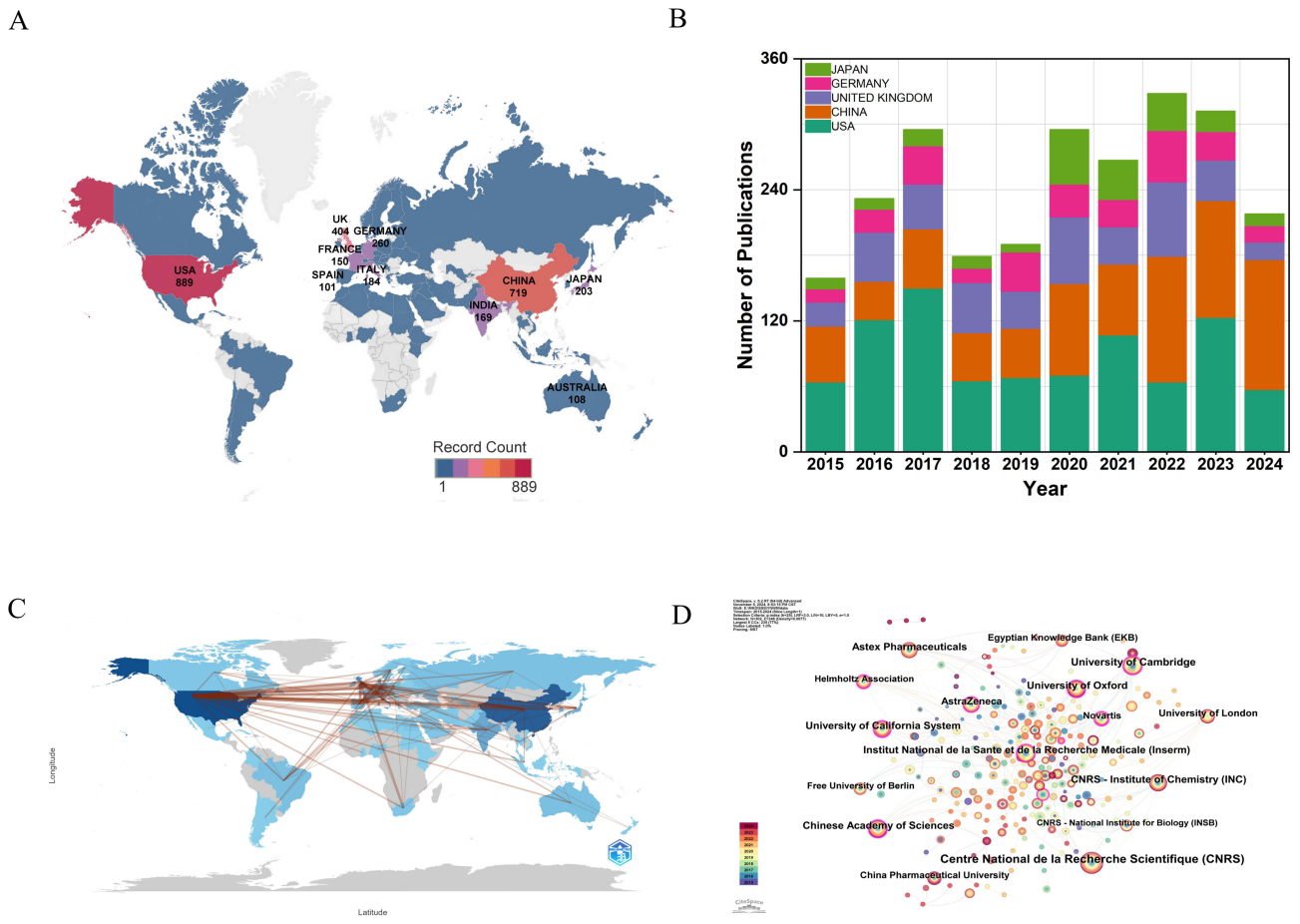

Figure 2 Visualization of countries and institutions involved in FBDD research (2015–2024). (**A**) Geographical distribution of FBDD research. (**B**) Annual research output of the top five countries in FBDD research. (**C**) Network of international collaboration, with more lines indicating deeper cooperation. (**D**) Institutional network, where each node represents an institution, and the size of the node reflects the number of publications.

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Figure 2C shows the international collaboration network in the FBDD research field, as mapped by Bibliometrix, which shows the scientific research collaborations between countries around the world. The different shades of blue on the map indicate the degree of participation of each country, with darker colors representing greater contributions. The number and complexity of the connections between countries indicate the intensity and breadth of cooperation, with more connections representing a more important position in international cooperation. As can be seen from the map, the United States, China, and European countries dominate this field. The United States has the highest level of participation and the most extensive cooperation network, maintaining close cooperation with many countries such as France, the United Kingdom, Canada, and Belgium, promoting academic exchanges and sharing research results. China is also active, collaborating not only with Asian countries such as Japan and South Korea, but also actively engaging in cross-regional collaborations with Europe and North America, enhancing its international influence. European countries such as France, Germany, and the United Kingdom collaborate closely with each other and maintain extensive exchanges with other regions. Australia also performs relatively well in the cooperation network, frequently collaborating with countries such as New Zealand, the United Kingdom, and Belgium. These collaborations have promoted knowledge exchange and innovation, enhanced the influence of each country in this field, and strengthened the breadth and depth of scientific discovery and knowledge sharing.

Analysis of Affiliated Institutions

The co-occurrence map of the institutions shows that a total of 302 research institutions established partnerships, forming 348 collaborative connections. In Figure 2D, each node represents an institution, and the size of the node is proportional to the number of publications, reflecting the research activity of the institution. Supplementary Table 1 lists the top 10 institutions with the most publications. Center National de la Recherche Scientifique (CNRS) ranked first with 47 publications, followed by the University of Cambridge (30 publications), the CNRS Institute of Chemistry (INC) (29 publications), the Chinese Academy of Sciences (29 publications) and the Institut National de la Sante et de la Recherche Medicale (Inserm) (29 publications). Nodes surrounded by a dark red ring indicate that these institutions have a high centrality of betweenness, indicating that they play a key role in connecting other nodes and promoting scientific research cooperation. The top five nodes in descending order of intermediary centrality are Novartis (0.2), Institut National de la Sante et de la Recherche Medicale (Inserm) (0.18), AstraZeneca (0.18), University of Cambridge (0.17), and University of Oxford (0.17). These highly centralized institutions act as important bridges in the network, promoting cooperation and exchanges between scientific research institutions.

Analysis of the Top Ten Influential Authors in FBDD Research

Based on data extracted from 1,301 documents, we identified the ten authors who have published the most articles (see Table 1; Figure 3). Among them, Abell C and Blundell TL ranked first with 14 articles each, demonstrating high academic productivity. They were followed by Johnson, CN, who published 13 articles and stood out for the number of citations, with

Table 1 Top 10 Authors Involved in FBDD Research Between 2015 and 2024

Rank*	Author	NP	TC	AC	H-index	LC	Rank†	Rank‡	Rank§	PY_start
1	Abell C	14	264	19	10	31	30	2	29	2015
2	Blundell TL	14	326	23	10	37	83	3	21	2016
3	Johnson CN	13	518	40	11	111	3	1	2	2015
4	De Esch IJP	13	248	19	9	66	89	6	6	2015
5	Zhang Y	13	221	17	7	5	105	13	769	2015
6	Scanlon MJ	12	180	15	7	25	144	15	50	2015
7	Chen YD	12	68	6	5	9	627	54	275	2015

(*Continued*)

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Table 1 (Continued).

Rank*	Author	NP	TC	AC	H-index	LC	Rank†	Rank‡	Rank§	PY_start
8	Von Delft F	11	448	41	9	39	7	5	19	2017
9	Li Y	11	127	12	7	12	174	16	164	2015
10	Wang L	11	146	13	7	4	222	17	1,005	2016

Abbreviations: NP, the number of publications; TC, the number of total citations; AC, the number of average citations of each record; H-index, Hirsch index; LC, the number of local citations; Rank*, Rank based on the NP; Rank†, Rank based on the TC; Rank‡, Rank based on the H-index; Rank§, Rank based on the local citations; PY_start, Publication year of the first article.

a total of 518 citations, showing the wide influence of his research. The average citation index (AC) of Johnson CN was 40, indicating a relatively high number of citations per article, which reflects the high academic recognition of his research results. In terms of the Hirsch index (H-index), Johnson CN's H-index is 11, significantly higher than that of other authors, indicating that his research has a high academic impact and sustained influence. Von Delft F and Blundell TL both have an H-index of 10, indicating that the research output of these two scholars has also been widely recognized by academia. Regarding the local citation count (LC), Johnson CN has an LC of 111, the highest among all authors, indicating that his research results are frequently cited in related literature and have a strong local influence. Zhang Y has an LC of 5, which is a relatively low local citation count but this may be related to the relatively small number of research publications, but his other indicators still indicate that his research results have a certain influence in the field. In terms of publication year, the research output of Abell C, Blundell TL, and Johnson CN began in 2015 and has continued to maintain high volumes. Von Delft F began research in 2017, and despite its late start, it has had a significant impact in the field with its high AC and LC; its research results have also had a significant impact in the field. Although Chen YD has published relatively few papers (only 12), his research has been cited 68 times overall, giving him an H-index of 5 and an LC of 9. These figures indicate that he has a certain degree of academic influence in the field. The performance of other authors such as Scanlon MJ, De Esch IJP,

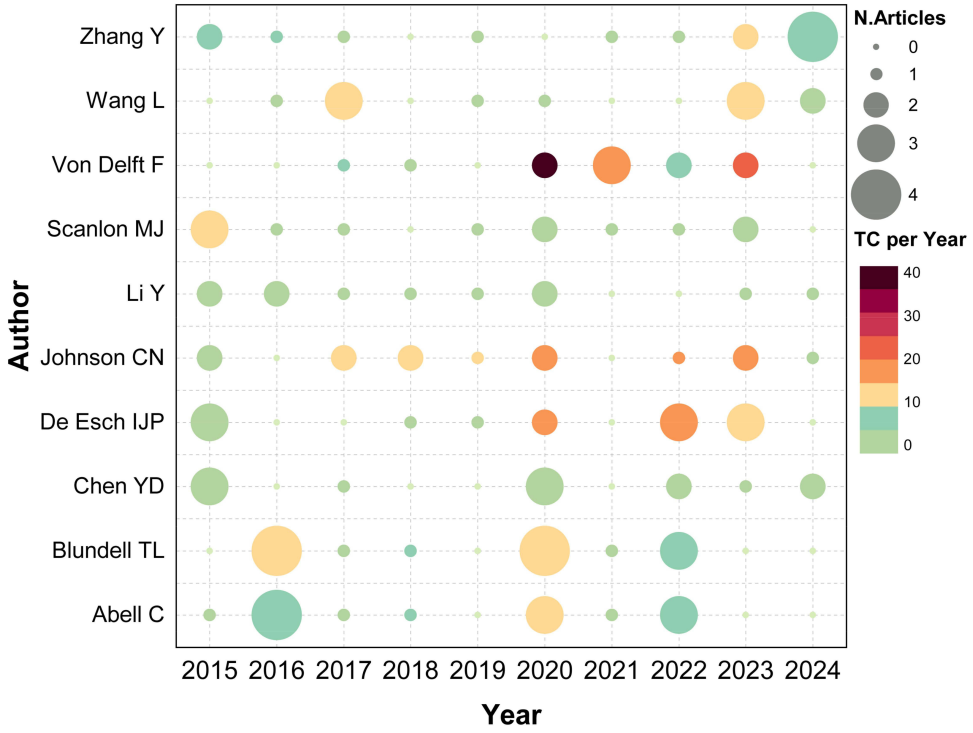

Figure 3 Annual publication output and citations of leading authors in FBDD research. The size of each circle represents the number of publications, whereas the color indicates the total number of citations per year for each author.

Table 2 Details of the Top ten Journals

Rank	Journal	Records (%)	TC	AC	IF	Quartile
1	*Journal of Medicinal Chemistry*	116(8.92%)	4,073	35	6.8	Q1
2	*Journal of Chemical Information and Modeling*	75(5.76%)	1,313	18	5.6	Q1
3	*European Journal of Medicinal Chemistry*	63(4.84%)	1,021	16	6	Q1
4	*Bioorganic & Medicinal Chemistry*	43(3.31%)	560	13	3.3	Q2
5	*Molecules*	38(2.92%)	302	8	4.2	Q2
6	*Acs Medicinal Chemistry Letters*	36(2.77%)	550	15	3.5	Q2
7	*ChemMedChem*	35(2.69%)	536	15	3.6	Q2
8	*Bioorganic & Medicinal Chemistry Letters*	34(2.61%)	484	14	2.5	Q2
9	*Journal of Biomolecular Structure & Dynamics*	30(2.31%)	303	10	2.7	Q2
10	*Bioorganic Chemistry*	23(1.77%)	239	10	4.5	Q1

Abbreviations: TC, the number of total citations; AC, the number of average citations of each record; H-index, Hirsch index; IF, Impact Factor; Quartile, Journal Citation Reports Quartile ranking.

and Wang L also reflects their contributions to FBDD research. Although they have published relatively few papers, they still stand out in terms of citations, AC, and LC. The analysis of the research output, citations, AC, H-index, and LC indicators of these scholars demonstrates their academic status and influence in the field of FBDD research.

Analysis of the Top Ten Journals

According to data extracted from the literature (see Table 2), the total number of records in the top ten journals represents 38.87% of the total publications in the research field. Among them, the *Journal of Medicinal Chemistry* ranked first with 116 articles and a total of 4,073 citations, showing its important influence in the field of FBDD research. It was followed by the *Journal of Chemical Information and Modeling* and the *European Journal of Medicinal Chemistry*, which published 75 and 63 papers, with 1,313 and 1,021 citations, respectively, indicating that they also have a high degree of attention in this field. In terms of AC, the *Journal of Medicinal Chemistry* ranked first with 35, showing the broad impact of its research results. The *Journal of Medicinal Chemistry* also led with an impact factor (IF) of 6.8, indicating its academic standing in the field. In addition, the high academic influence the *European Journal of Medicinal Chemistry* and the *Journal of Chemical Information and Modeling* are also reflected by their respective IFs of 6.0 and 5.6. According to the Journal Citation Reports division, the above journals are all classified in Q1, whereas journals such as *Bioorganic & Medicinal Chemistry, Molecules* and *ChemMedChem* are in Q2, indicating that they also have a strong influence in the field of FBDD research. Overall, the top ten journals have outstanding performance in terms of publication volume, number of citations, AC, and IF, which fully demonstrates their academic dominance in this research field.

Keywords and Trend Topics Analysis

In this study, a total of 3,020 keywords were extracted using VOSviewer software, of which 94 keywords that appeared more than 5 times were selected for visual analysis. Figure 4A shows the density visualization of keyword co-occurrences, where the darkness of the color reflects the density, ranging from 0 (white) to 0.5 (blue) and 1 (red). This visualization highlights "fragment-based drug design" as the main keyword, followed by "fragment-based drug discovery", "molecular docking" and "drug discovery." Keyword clustering is a method of grouping keywords based on their thematic similarity. Using CiteSpace software, nine relevant clusters were identified: virtual screening, fragment-based drug design, affinity, crystal structure, drug discovery, molecular simulation, mycobacterium tuberculosis, alchemical free energy calculations and ligand binding (Figure 4B).

The results of the cluster analysis in this study revealed nine main research clusters. The first cluster focused on virtual screening, molecular modeling, and the design of antitumor drugs, emphasizing molecular docking and drug discovery as key research areas. The second cluster focused on FBDD, dynamic combinatorial chemistry, protein inhibition mechanisms, and the incorporation of machine learning (ML) techniques. The third group focused on drug discovery and design, especially protein affinity and drug selection mechanisms. The fourth cluster explored drug design,

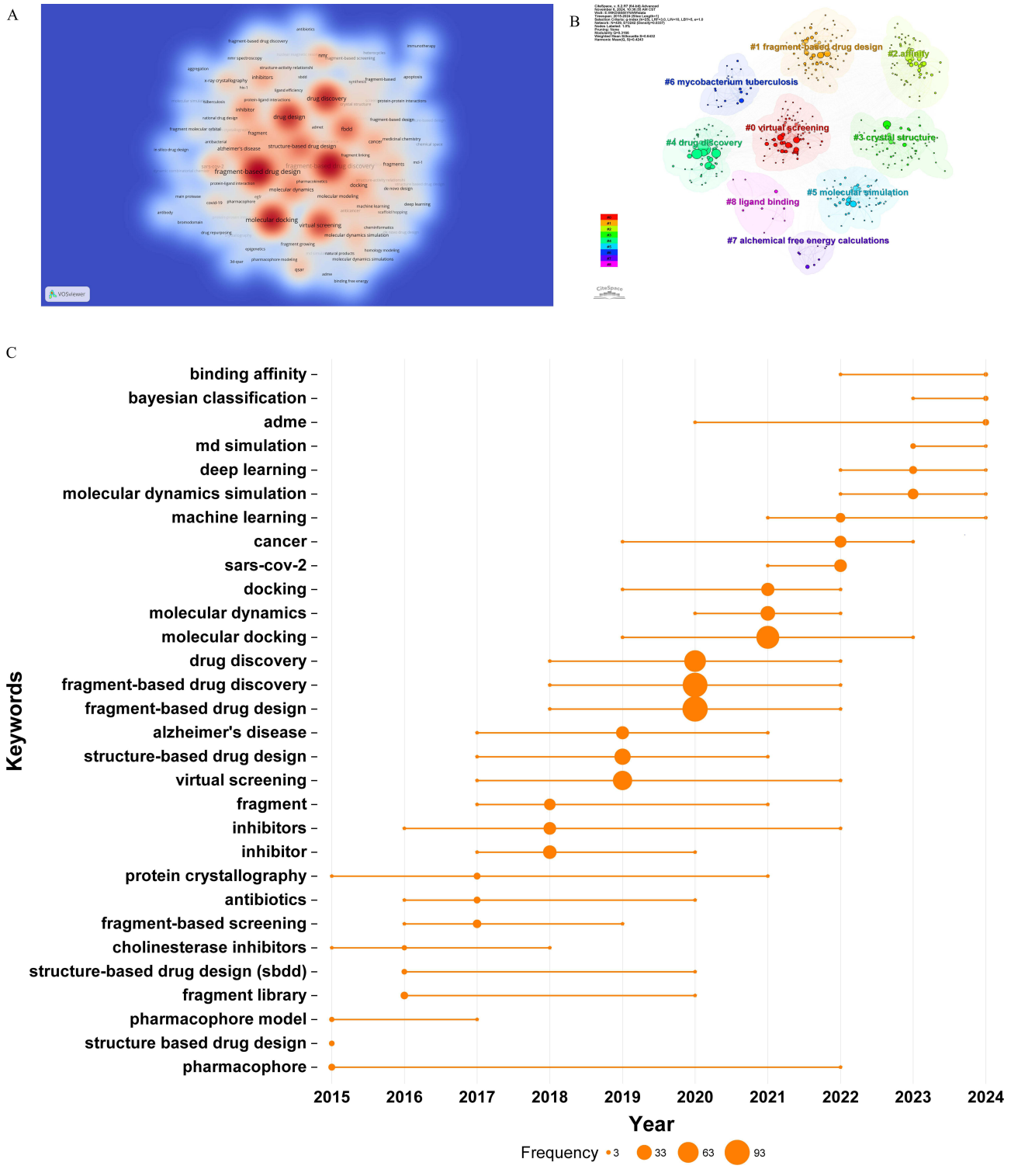

Figure 4 Keyword analysis visualization in FBDD research (2015–2024). (**A**) Density map showing the frequency of keyword occurrences, where densities of 0, 0.5, and 1 are represented by white, blue, and red colors, respectively. (**B**) Keyword cluster map representing various research topics visualized using CiteSpace. (**C**) Trend plot illustrating the evolution of key topics based on keyword changes. The size of the circles reflects keyword occurrence frequency, whereas the Orange line indicates the duration of each keyword's presence.

tumor microenvironment, and inhibition of protein–protein interactions, with research into Alzheimer's disease. The fifth cluster focused on drug discovery, fragment selection, and inhibitor design, with a particular focus on the affinity and activity of inhibitors. The sixth group examined molecular docking, molecular orbitals, molecular simulations, and their application in the design of antimicrobial agents, especially under the action of the main protease. The seventh group focused on drug design, molecular dynamics, and their effects on drug efficacy, especially in the study of mechanically sensitive channels. The eighth cluster explored fragment-based drug discovery, molecular screening, and their applications in drug permeability and binding. The ninth cluster focused on tuberculosis drug design and molecular screening, exploring their efficacy against molecular targets and enzymes. These clusters demonstrated diverse research directions in the fields of FBDD, molecular screening, drug discovery, and optimization.

Keyword evolution analysis revealed the frequency of occurrence of multiple key terms and their temporal trends (Figure 4C). Early research focused on keywords such as "pharmacophore", "structure-based drug design (SBDD)", and "pharmacophore model", a model which appeared primarily in 2015–2016, reflecting the initial exploration of drug design during this period. In the following years, keywords related to drug discovery gradually appeared, such as "fragment-based screening", "antibiotics", "protein crystallography", and "inhibitors." The median year of these keywords was concentrated between 2016 and 2018, indicating that research has gradually deepened into the application of fragment screening and protein crystallography. From 2018 onward, keywords such as "fragment-based drug design,:"-fragment-based drug discovery", and "drug discovery" gradually became the main research directions, with high frequencies, reflecting the widespread application and emphasis of FBDD methods in the field of drug design. Subsequently, keywords such as "molecular docking", "molecular dynamics", and those related to Alzheimer's disease gradually appeared, with a focus on the period from 2019 to 2021, reflecting the expansion of research directions toward disease targets and molecular simulation methods during this period. In recent years, especially since 2021, keywords such as "SARS-CoV-2", "ML", "deep learning", and "molecular dynamics simulation" gradually become research hotspots. The median year of appearance of these keywords concentrated between 2022 and 2024, reflecting the gradual application of ML and deep learning in drug design and screening. Furthermore, "md simulation", "Bayesian classification" and "binding affinity" were also keywords that occurred frequently between 2023 and 2024, showing the growing interest in simulation technology and statistical methods in the field of drug discovery.

Top Ten Cited Publications and Co-Cited Reference Bursts

Among the literature related to FBDD, the 10 best-cited publications covered a wide range of research fields from drug design to fragment detection (Table 3). The study "The FTMap family of web servers for determining and characterizing ligand-binding hot spots of proteins" by Kozakov D et al published in *Nature Protocols* in 2015, with 434 citations, ranked first, which fully demonstrates its importance in ligand ligand-binding hot spot analysis.[31] Śledź P et al published a study in 2017 in *Current Opinion in Structural Biology*, entitled "Protein structure-based drug design: from docking to molecular dynamics", which received 359 citations, reflecting its important contribution to structure-based drug design.[32] Proschak E et al, published "Polypharmacology by design: A medicinal chemist's perspective on multitargeting compounds" in 2019 in the *Journal of Medicinal Chemistry*, in which the authors discussed the importance of multitarget drug design in medicinal chemistry with 317 citations, promoting the multi-targeted applications of FBDD.[33] Gupta A et al, in their publication entitled "Generative recurrent networks for de novo drug design" published in *Molecular Informatics* in 2018 has received 286 citations, demonstrating the gradual application and recognition of ML and artificial intelligence (AI) in the field of drug design.[34] Kessler D et al received 267 citations to their study "Drugging an undruggable pocket on KRAS" published in the *Proceedings of the National Academy of Sciences of the United States of America* in 2019. This further demonstrates the focus on challenging targets in cancer research and the importance of FBDDs in cancer treatment.[35] The study by Zhou J et al 2018, entitled "Highly emissive self-assembled BODIPY-platinum supramolecular triangles" in the *Journal of The American Chemical Society*, with 208 citations, demonstrated the potential of FBDDs in the application of new optical materials.[36] In addition, Douangamath A et al, published in 2020, a study entitled "Crystallographic and electrophilic fragment screening of the SARS-CoV-2 main protease" in *Nature Communications*, which has received 206 citations, demonstrating its contribution to antiviral drug discovery.[37] The study by Gao X et al from 2021, entitled, "Crystal structure of SARS-CoV-2 papain-like protease", published in *Acta*

Table 3 Top 10 Articles Frequently Referenced on a Global Scale

Title	First Author	Year	Journal	IF (JCR)	Global Citations
The FTMap family of web servers for determining and characterizing ligand-binding hot spots of proteins[31]	Kozakov D	2015	*Nature Protocols*	13.1(Q1)	434
Protein structure-based drug design: from docking to molecular dynamics[32]	Śledź P	2017	*Current Opinion in Structural Biology*	6.1(Q1)	359
Polypharmacology by design: A medicinal chemist's perspective on multitargeting compounds[33]	Proschak E	2019	*Journal of Medicinal Chemistry*	6.9(Q1)	317
Generative recurrent networks for de novo drug design[34]	Gupta A	2018	*Molecular Informatics*	2.8(Q2)	286
Drugging an undruggable pocket on KRAS[35]	Kessler D	2019	*Proceedings of The National Academy of Sciences of The United States of America*	9.4(Q1)	267
Highly emissive self-assembled BODIPY-platinum supramolecular triangles[36]	Zhou J	2018	*Journal of The American Chemical Society*	14.5(Q1)	208
Crystallographic and electrophilic fragment screening of the SARS-CoV-2 main protease[37]	Douangamath A	2020	*Nature Communications*	14.7(Q1)	206
Crystal structure of SARS-CoV-2 papain-like protease[38]	Gao X	2021	*Acta Pharmaceutica Sinica B*	14.8(Q1)	200
Design principles for fragment libraries: maximizing the value of learnings from pharma FBDD programs for use in academia[39]	Keserű GM	2016	*Journal of Medicinal Chemistry*	6.9(Q1)	167
Dipicolinic Acid derivatives as inhibitors of New Delhi metallo-β-lactamase-1[40]	Chen AY	2017	*Journal of Medicinal Chemistry*	6.9(Q1)	134

Pharmaceutica Sinica B, has received 200 citations, demonstrating the importance of in-depth research on the structure of coronavirus targets.[38] Keserű GM published a study entitled "Design principles for fragment libraries: Maximizing the value of learnings from pharma FBDD programs for ese in academia", in the *Journal of Medicinal Chemistry* in 2016, which has received 167 citations, highlighting the value of applying the pharmaceutical industry's FBDD experience to academic research.[39] Finally, the study "Dipicolinic acid derivatives as inhibitors of New Delhi metallo-β-lactamase-1" by Chen AY et al published in the *Journal of Medicinal Chemistry* in 2017 has received 134 citations, demonstrating the broad prospects of FBDD in the development of antibacterial drugs.[40]

To provide more practical and content-focused information, we also analyzed the top 10 most cited publications in the FBDD field between 2015 and 2024. These articles span a wide range of target types and therapeutic areas, including kinase inhibitors, viral protease inhibitors, and metalloenzyme modulators. Table 4 highlights the screening technologies, fragment optimization strategies, and key contributions each study made to modern drug discovery.

Based on the citation burst analysis, the top 25 references with the most significant citations in the field of FBDD are shown in Figure 5. Erlanson DA et al published in *Topics in Current Chemistry in 2012* a paper with the highest citation strength between 2015 and 2017, reaching a score of 11.02, reflecting the impact of this literature at an early stage.[41] In additions, the studies published between 2015 and 2017, by Scott DE et al in *Biochemistry-US* and Murray CW et al in *Trends in Pharmacological Sciences achieved* high citation bursts of 10.6 and 10.19, respectively[42,43] The study by Baker M published in *Nature Reviews. Drug Discovery* in 2013 attracted considerable attention between 2015 and 2018, with an intensity of 9.44[44] Other papers with high citation bursts include the study by Joseph-McCarthy D et al published in *Journal of Chemical Information and Modeling* in 2014, which had a citation burst from 2015 to 2018 with an intensity of 7.74 and the study by Hopkins et al al published in in *Nature Reviews. Drug Discovery* in 2014, with a citation surge lasting until 2019 and an intensity of 7.68.[45,46] In addition, the research of Erlanson DA et al published in *Nature Reviews. Drug Discovery* in 2016 showed its importance during the period from 2017 to 2021, with the highest surge intensity of 26.86[47] Between 2021 and 2024, Kirsch P et al and Jumper J et al caused relatively significant citation bursts, with their studies published in *Molecules* and *Nature*, with citation burst strengths of 9.57 and 6.73, respectively, reflecting the influence of these studies in the modern field of FBDD.[9,48]

Table 4 Target Types, Screening Strategies, and Optimization Approaches in the Top 10 Most Cited FBDD Publications

Reference Number	Target Type & Disease Area	Screening / Computational Method	Optimization Strategy	Key Contribution
Kozakov 2015[31]	Various protein structures (hotspot mapping)	Structure-based virtual screening (FTMap)	Hotspot identification for fragment placement	FTMap enables fast and accurate binding hotspot prediction
Śledź 2018[32]	General protein targets	Docking + Molecular Dynamics (MD)	Binding conformation prediction	Improves prediction of binding poses and affinities
Proschak 2019[33]	Multitarget compounds (cancer, inflammation)	In vitro profiling + structure-guided tools	Designed polypharmacology	Framework for rational multitarget drug design
Gupta 2018[34]	AI-based molecular generation (multiple targets)	Generative RNN-LSTM (SMILES generation)	Transfer learning + low-data fine tuning	AI-enhanced low-data de novo molecule generation
Kessler 2019[35]	KRAS (oncogenic, PPI)	Structure-based design + X-ray	Fragment growing (BI-2852)	Breakthrough in drugging KRAS via novel pocket
Zhou 2018[36]	Pt-based supramolecular anticancer agents	Self-assembly + cell assay + microscopy	Modular design for PDT + chemotherapy	Multifunctional anticancer theranostic agents
Douangamath 2020[37]	SARS-CoV-2 Main Protease (COVID-19)	Crystallography + electrophilic fragment screening	Fragment merging (covalent + non-covalent)	Rapid SARS-CoV-2 inhibitor discovery platform
Gao 2021[38]	SARS-CoV-2 Papain-like Protease (COVID-19)	X-ray + ligand-bound structural analysis	Structure-guided inhibitor refinement	Reveals inhibition mechanism for viral protease
Keserű 2016[39]	General proteins (fragment library design)	Industry experience + theoretical guidance	Library design (size, shape, properties)	Bridges pharma FBDD insights to academia
Chen 2017[40]	NDM-1 Metallo-β-lactamase (antibiotic resistance)	FBDD + EPR/NMR validation	SAR development + ternary complex stabilization	New NDM-1 inhibitors combating drug resistance

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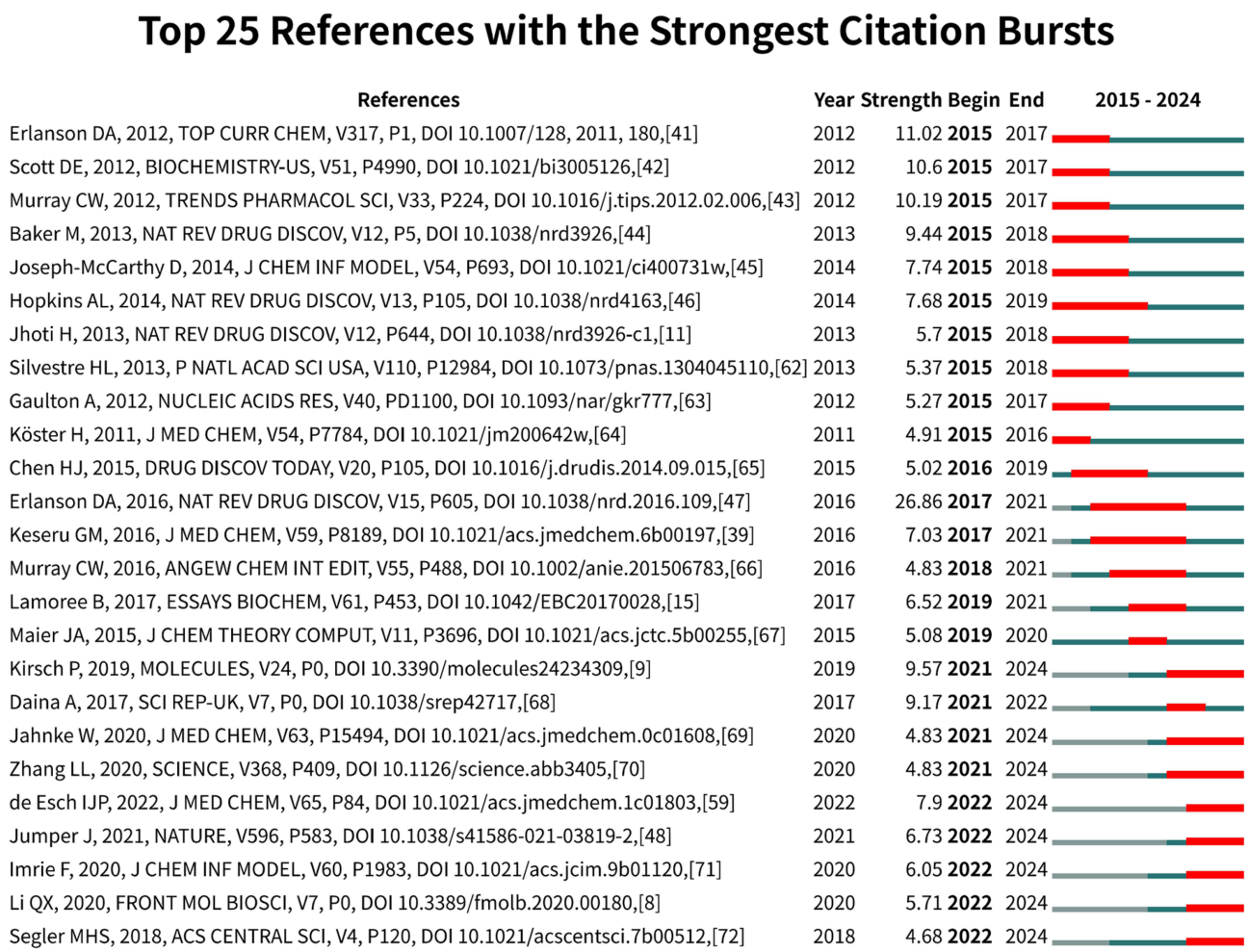

Figure 5 Top 25 co-cited references with the strongest citation bursts. The timeline is represented by a dark blue line, with red segments indicating the duration of citation bursts, showing the start year, end year, and length of the burst. The light blue segments represent years when the reference had not yet been published.

Discussion

This study systematically analyzed academic literature in the field of FBDD from 2015 to 2024 using bibliometric methods, with the aim of revealing research trends, major contributors, core journals, and future directions of development in this field. This discussion will comment on the research results in depth from multiple dimensions, analyze the current state of development of FBDD and its importance in drug research and development, and propose potential directions and suggestions for future research.

From 2015 to 2024, the number of FBDD-related publications generally showed a fluctuating upward trend, with an average annual growth rate of 1.42%. In particular, the number of publications reached a peak of 142 in 2020, which may have been related to global health events (such as the COVID-19 pandemic) that have driven urgent needs in the field of drug research and development.[49] FBDD, as an efficient drug discovery strategy, has shown its unique advantages in responding to public health emergencies.[50,51] For example, the fragment screening study targeting the main protease of SARS-CoV-2 published by Douangamath A et al in 2020 demonstrates the application potential of FBDD in responding rapidly to emerging viral threats.[37] However, despite the overall upward trend, the number of citations in recent years (especially 2023 and 2024) has decreased significantly. There may be multiple reasons for this: first, recent papers have

not yet accumulated enough citations; second, the field of FBDD may be facing a shift in research hotspots, with emerging technologies such as AI-driven drug design beginning to receive more attention, leading to a slowdown in the growth of citations for traditional FBDD research. In addition, the uneven quality of the research may also affect the steady growth of citations.[52,53] Therefore, improving the quality of research and ensuring innovation and practicality remain urgent issues to address in the field of FBDD.

Approximately 34.82% of articles related to FBDD involve international collaboration, reflecting the global nature of the field. International collaboration not only promotes the sharing of resources and knowledge but also accelerates the transformation and application of technology. For example, the United States and China have dominated FBDD research, and there is frequent collaboration between the two countries, which has helped promote the rapid development and wide application of FBDD technology. In addition, close cooperation between European countries, such as France, Germany, and the United Kingdom, has also provided a solid foundation for interdisciplinary research in the field of FBDD. High levels of international collaboration are often accompanied by higher research output and greater academic impact. Through cross-border collaboration, research teams can integrate the advantageous resources of different regions, conduct large-scale joint research projects, and improve the depth and breadth of research. However, international collaboration also faces challenges such as cultural differences, uneven resource allocation, and intellectual property protection. For example, differences in research funding, research ethics, and data sharing in different countries can affect the efficiency of cooperation and the sharing of results. Therefore, future FBDD research should continue to strengthen international cooperation and exchanges and establish more efficient and transparent cooperation mechanisms to address complex issues in global drug research and development.

This study identified institutions such as the CNRS, the University of Cambridge, and the Chinese Academy of Sciences as having significant research output and influence in the field of FBDD. These institutions have not only published a large number of high-quality research papers but have also played an important role in promoting the development and application of FBDD technology. Highly centralized companies such as Novartis and AstraZeneca, as pharmaceutical giants, have further promoted the practical application of FBDD in drug development through their strong research and development capabilities and resources. The successful experience of these institutions shows that a strong scientific research infrastructure, sufficient research funding, and interdisciplinary research teams are key factors in promoting the development of the field of FBDD. For example, the CNRS has promoted the innovation and application of FBDD technology through its multidisciplinary research platform, which integrates experts in fields such as chemistry, biology, and computational science.[54] The University of Cambridge, with its advanced structural biology technology, has provided high-resolution target protein structures for FBDD, which has promoted the precision of the fragment screening and optimization process.[18] In the future, other research institutions should learn from the successful models of these leading institutions, strengthen their internal scientific research capabilities, and enhance international cooperation to achieve greater breakthroughs in FBDD research. Furthermore, promoting close collaboration between academia and industry and facilitating the translation of the results of the basic research into practical drug development are also important ways to enhance the impact of FBDD research.

In the field of FBDD, authors such as Abell C and Blundell TL have become leaders in the field with high output and citation rates. Their research not only has had a significant academic impact but has also provided important theoretical support for the optimization and application of FBDD methods. For example, the studies by Abell C et al on fragment screening and structure optimization has provided systematic guidance for subsequent drug subsequent drug design.[55,56] Blundell TL has made outstanding contributions in the elucidation of protein–fragment interactions, promoting the application of FBDD in target identification and fragment optimization.[57,58] Additionally, Johnson CN has demonstrated widespread recognition and continued influence in academia through his high H-index and local citations.[59] These high-impact authors have provided a solid theoretical foundation and practical guidance for the development of FBDD technology through systematic research and innovative methods. Their research results have not only promoted the continuous optimization of the FBDD method but have also promoted the wide application of FBDD to different disease targets. To further improve the level of research in the field of FBDD, more researchers with interdisciplinary backgrounds and innovative capabilities should be cultivated in the future. For example, interdisciplinary talents combining chemistry, structural biology, and computational science will help promote the multidimensional development of FBDD

technology. Furthermore, encouraging young researchers to participate in international collaborative projects and gain more research experience and resource support is also an important strategy to improve the overall level of FBDD research.

Journals such as the *Journal of Medicinal Chemistry*, the *Journal of Chemical Information and Modeling*, and the *European Journal of Medicinal Chemistry* dominate the field of FBDD and have published a large number of high-quality research papers. These journals not only have high IF but also enjoy wide recognition in academia and have become important platforms for publishing FBDD research results. High-quality academic communication helps promote the rapid dissemination and application of research results and promote the widespread application of FBDD technology in drug research and development. However, an overly concentrated publication channel can also lead to a limited research perspective. Researchers who rely too heavily on a few core journals may overlook other potentially important research results and developments in emerging fields. Therefore, encouraging researchers to publish their research results in a wider range of journals can help expand the scope of application of FBDD research and promote interdisciplinary exchanges and cooperation. Additionally, the rise of open access journals and preprint platforms has also provided more diverse academic communication channels for FBDD research, improving the visibility and impact of research results.

Through keyword co-occurrence analysis, keywords such as "fragment-based drug discovery", "molecular docking", and "drug discovery" frequently appeared, reflecting the core direction of FBDD research. At the same time, with the development of technology, emerging keywords such as "artificial intelligence" and "machine learning" have gradually become research hotspots. This indicates that FBDD research is gradually moving toward a more efficient and intelligent direction, integrating advanced computational techniques to improve the efficiency and accuracy of drug discovery. For example, the research published in 2018 by Gupta A et al entitled "Generative recurrent networks for de novo drug design" demonstrated the potential of generative recurrent neural networks in new drug design, promoting the integration of FBDD and AI technology.[34] In addition, the appearance of disease-related keywords such as "mycobacterium tuberculosis" and "Alzheimer's disease" shows that FBDD has important application prospects in the development of drugs targeting specific diseases. In particular, in the development of antibacterial drugs and drugs for neurodegenerative diseases, the FBDD method has improved drug selectivity and affinity by optimizing fragment structures and has promoted the drug research and development process for complex diseases. In the future, in combination with precision medicine and personalized treatment, FBDD is expected to play a greater role in drug research and development for complex diseases. For example, by integrating patient genomic data and molecular mechanisms of disease, FBDD can design more personalized and targeted drugs to improve treatment outcomes and reduce side effects.

The most cited literature covers a wide range of topics, from ligand-binding hotspot analysis, structure-based drug design, and multitarget drug design, to the application of ML in drug design. These highly cited articles provide cutting-edge directions and important breakthroughs in FBDD research and have promoted the rapid development of this field. For example, the research on ligand-binding hotspots by Kozakov D et al provided important theoretical support for FBDD;[31] the multitarget drug design explored by Proschak E et al broadens the scope of FBDD in the treatment of complex diseases.[33] The analysis of citation bursts further revealed the hot topics and emerging trends in FBDD research, such as the application of AI in drug design and the development of drugs targeting specific pathogens. These research hotspots reflect the key role of FBDD technology in addressing emerging health challenges and also suggest potential directions for future research. For example, the introduction of AI technology has made fragment screening and optimization processes of FBDD more efficient and precise, promoting the automation and intelligent development of drug discovery. Furthermore, the development of drugs for emerging pathogens such as SARS-CoV-2 demonstrates the important application value of FBDD in addressing global health crises.

Despite the continuous advancement of technology, especially the integration of AI and big data analysis technology, FBDD is expected to play a more important role in drug research and development.[60,61] In the future, combined with precision medicine and personalized treatment, FBDD will further expand its scope of application and help to accelerate the development and marketing of new drugs. Researchers and pharmaceutical companies should strengthen cooperation to optimize research methods and improve the application efficiency and success rate of FBDD technology to promote the sustainable development of global drug research and development. Additionally, policy support and investment in research funding are also key factors in promoting the continued development of the FBDD field. Governments and

relevant institutions should increase support for FBDD research, encourage interdisciplinary and cross-institutional collaborative research, and promote the innovation and application of FBDD technology. At the same time, establishing a sound intellectual property protection mechanism to protect the legitimate rights and interests of research results will also help attract more researchers and enterprises to participate in FBDD research and development. Finally, with the continuous development of the biomedical field, FBDD will play an increasingly important role in the management of emerging diseases and complex pathological mechanisms. By continuously optimizing fragment screening and optimization processes, combined with advanced structural biology and computational chemistry techniques, FBDD will provide more efficient and precise tools for drug discovery and promote new drug research and development to a new level.

Although this study comprehensively analyzed the current research status in the field of FBDD through bibliometrics, some limitations should be acknowledged. First, the data source was limited to the WOSCC, which may not have covered all relevant literature, especially study results in preprints and open access journals, which have developed rapidly in recent years. Second, bibliometric analysis is heavily based on quantitative indicators and does not explore the quality of research and the effectiveness of practical applications in depth. Additionally, due to the rapid development of FBDD technology, some of the most recent research results may not have been fully included or analyzed. Future research should consider integrating more database resources, such as Scopus, PubMed, and Google Scholar, to obtain more comprehensive data from the literature. In addition, a combination of qualitative and quantitative analysis methods, such as content analysis and topic modeling, should be used to gain deeper research insights. Furthermore, focusing on the application cases of FBDD technology in actual drug development and evaluating its effectiveness and potential in different areas of disease will help better understand the practical value of FBDD in drug research and development. For example, case studies that analyze the successes and challenges of FBDD in specific drug development can provide valuable references for future research and practice.

Conclusion

This bibliographic study provides a concise overview of research in the field of FBDD from 2015 to 2024. The findings reveal steady growth in publications, with the United States and China as the main contributors and strong international collaborations. Influential institutions and authors have driven progress in fragment selection, optimization, and application. Research trends have shown a shift toward AI-assisted drug design, molecular simulations, and expanded disease targets, including cancer, neurodegeneration, and COVID-19. Despite challenges such as weak binding affinities and hit-to-lead conversion, FBDD remains a vital strategy in modern drug discovery. This study offers valuable information to guide future research and innovation in the field.

Abbreviations

AC, Average citation; AI, Artificial intelligence; CNRS, Center National de la Recherche Scientifique; FBDD, Fragment-based drug design; FBLD, Fragment-based lead discovery; ITC, Isothermal titration calorimetry; LC, Local citation count; ML, Machine learning; NMR, Nuclear magnetic resonance; SAR, Structure-activity relationship; SPR, Surface plasmon resonance; TC, Total citations; TSA, Thermal shift assays; WOSCC, Web of Science Core Collection.

Data Sharing Statement

No datasets were generated or analyzed during the current study.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no competing interests in this work.

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