ACUMEN: INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH
ISSN: 3060-4745 IF(Impact Factor)10.71 / 2025 Volume 3, Issue 4

CODE, CURE, REPEAT: AI REDEFINING ANTIBIOTIC TREATMENT

keywords: artificial intelligence, antibiotic discovery, antimicrobial resistance, deep learning, drug repurposing, halicin, abaucin, machine learning, pharmaceutical innovation, superbugs

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Introduction

In 1928, Alexander Fleming returned to his laboratory at St. Mary's Hospital to find a mold-contaminated petri dish that would forever change medicine. That serendipitous moment—penicillin's discovery—ushered in the antibiotic era, transforming once-fatal bacterial infections into manageable ailments. For decades, the pharmaceutical industry relied on a similar playbook: soil screening, natural product extraction, and semi-synthetic modifications. Yet this golden age has long since faded. The pipeline of new antibiotics has dried to a trickle, while pathogenic bacteria have evolved into multidrug-resistant superbugs that render our existing arsenal increasingly obsolete .

Today, humanity faces a paradox. We possess more biomedical knowledge than ever before, yet we are losing the arms race against microbes. The World Health Organization now warns that antimicrobial resistance (AMR) is outpacing advances in modern medicine, with one in six laboratory-confirmed bacterial infections worldwide resistant to antibiotic treatments as of 2023 . Between 2018 and 2023, resistance rose in over 40% of pathogen-antibiotic combinations monitored globally, climbing at an

average annual rate of 5–15% . In this bleak landscape, a new protagonist has emerged—not from a petri dish, but from lines of code.

Artificial intelligence is redefining antibiotic treatment by collapsing the timelines of discovery from decades to days, by seeing molecular patterns invisible to human chemists, and by resurrecting forgotten compounds from digital graveyards. This narrative explores how machine learning algorithms have become the modern world's antibiotic hunters, tracing the journey from the first AI-discovered molecule, Halicin, to the narrow-spectrum precision of Abaucin, and onward to a future where generative models design de novo antibiotics tailored to specific pathogens. The story is one of code, cure, and the relentless repetition of scientific iteration—only now, the iteration happens at silicon speed.

The Silent Pandemic: Antibiotic Resistance in the 21st Century

To appreciate the urgency of AI-driven discovery, one must first understand the scale of the crisis. Antimicrobial resistance is not a distant threat; it is a present-tense catastrophe. The WHO's *Global Antibiotic Resistance Surveillance Report 2025* presents a harrowing portrait: resistance is highest in the South-East Asian and Eastern Mediterranean Regions, where one in three reported infections defy conventional antibiotics, while in the African Region, one in five infections is resistant . Even in well-resourced health systems, carbapenem-resistant *Enterobacteriaceae*, methicillin-resistant *Staphylococcus aureus* (MRSA), and pan-resistant *Acinetobacter baumannii* have turned hospital wards into high-stakes battlegrounds.

Figure 1: Drug-resistant bacterial pathogens represent one of the greatest threats to global health security. (Image: Broad Institute)

The economic and human toll is staggering. Traditional drug discovery is a marathon of diminishing returns. Between 2000 and 2015, 86% of drug candidates failed to meet planned targets, generating a stagnation in antibiotic research that began in the 1980s . Unlike chronic disease therapeutics—where blockbuster drugs promise sustained revenue—antibiotics offer poor financial returns, discouraging pharmaceutical investment. A single antibiotic can require $1 billion to $2 billion in development costs

and up to 15 years from bench to bedside . Meanwhile, bacteria evolve resistance in a fraction of that time. The result is an innovation desert, where the last truly novel antibiotic classes were discovered before the rise of the personal computer.

From Serendipity to Silicon: The Evolution of Drug Discovery

For most of the twentieth century, antibiotic discovery was a game of chance. Scientists screened soil microbes, fermented broths, and tested extracts against pathogenic cultures. This empirical approach yielded spectacular successes—streptomycin, tetracyclines, macrolides—but it was laborious, expensive, and ultimately exhausted the low-hanging fruit of easily culturable microorganisms. By the 1990s, pharmaceutical companies were rediscovering the same scaffolds with minor modifications, while true novelty remained elusive.

The digital revolution offered a way out. High-throughput screening (HTS) allowed researchers to test thousands of compounds simultaneously, yet the chemical space of possible drug-like molecules—estimated at 10^60—remained laughably out of reach. Human intuition, no matter how refined, could not navigate this expanse. Enter artificial intelligence. With its capacity to process vast datasets, identify non-obvious patterns, and generalize from limited examples, AI transformed the discovery paradigm from brute-force searching to intelligent prediction .

Modern AI-driven drug discovery rests on three pillars: representation, prediction, and generation. *Representation* involves encoding molecular structures into formats machines can understand—molecular graphs, fingerprints, or sequence embeddings. *Prediction* uses trained models to forecast biological activity, toxicity, or pharmacokinetic properties. *Generation* employs generative models to create entirely new molecules optimized for desired criteria. Together, these capabilities allow researchers to explore chemical space with unprecedented efficiency, turning the traditional discovery funnel into a targeted, computationally guided missile.

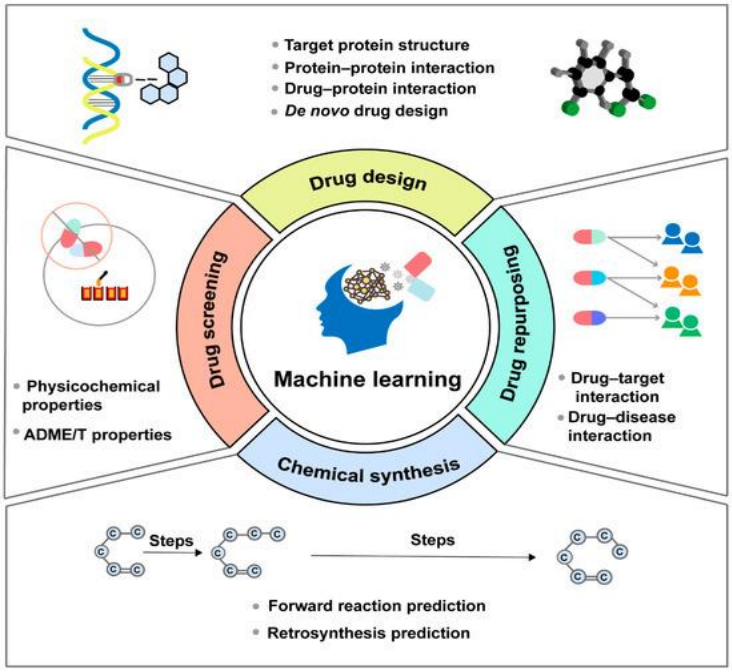

Figure 2: Machine learning applications across the drug discovery pipeline, from target identification to chemical synthesis. (Image: MDPI Molecules)

The Algorithmic Alchemist: How AI Discovers Antibiotics

At the heart of AI's antibiotic revolution lies deep learning—a class of neural network architectures capable of learning hierarchical features from raw data. Unlike traditional quantitative structure-activity relationship (QSAR) models, which rely on hand-engineered molecular descriptors, deep learning constructs its own representations, capturing subtle structural nuances that correlate with antibacterial activity.

The landmark 2020 study by Stokes et al. exemplifies this approach. The researchers trained a directed-message passing neural network (D-MPNN) on just 2,335 molecules— a modest training set by modern standards—to predict growth inhibition of *Escherichia coli* . The model translated molecular graphs into continuous vectors by passing "messages" along chemical bonds, iteratively aggregating information about neighboring atoms to construct higher-level substructure representations. Augmented with RDKit molecular features and optimized through Bayesian hyperparameter search, the ensemble model achieved a robust ROC-AUC of 0.896 on held-out test data .

What happened next was extraordinary. The trained model was unleashed on the Drug Repurposing Hub—a library of 6,111 molecules at various stages of clinical investigation. Within days, it ranked compounds by predicted antibacterial probability. Of the top 99 predictions, 51 were validated as true positives in laboratory assays—a

hit rate that would be unimaginable in random screening . Among these, one molecule stood out: SU3327, a c-Jun N-terminal kinase inhibitor previously investigated for diabetes. Renamed Halicin, this compound displayed potent bactericidal activity against a wide phylogenetic spectrum, including carbapenem-resistant Enterobacteriaceae and pan-resistant *Acinetobacter baumannii* .

The methodology has since proliferated. Table 1 summarizes the principal AI techniques currently deployed in antibiotic discovery, their mechanisms, and representative applications.

Table 1: AI Techniques in Antibiotic Discovery

Technique	Mechanism	Key Application	Representative Example
Directed-Message Passing Neural Networks (D-MPNN)	Passes messages along molecular bonds to encode graph structures into continuous vectors	Predicting growth inhibition from molecular structure	Halicin discovery from Drug Repurposing Hub
Convolutional Neural Networks (CNN)	Applies convolutional filters to spatial data such as protein structures or cell images	Phenotypic screening and resistance detection	Single-cell antimicrobial susceptibility testing
Recurrent Neural Networks (RNN) / Transformers	Processes sequential data using attention mechanisms	Peptide antibiotic prediction from sequence	APEX model for mining extinct proteomes

Technique	Mechanism	Key Application	Representative Example
Generative Adversarial Networks (GANs)	Pitits generator against discriminator to create novel molecules	De novo antibiotic design	Generative AI for novel *A. baumannii* inhibitors
Reinforcement Learning	Optimizes molecular properties through reward-driven exploration	Multi-objective optimization of potency and synthesizability	Scaffold optimization in lead generation
Variational Autoencoders (VAE)	Learns latent representations of molecular space for interpolation and generation	Exploring chemical space between known active compounds	Novel antibacterial scaffold generation

These techniques share a common advantage: they collapse the time required for early-stage discovery from years to hours. Screening 107 million compounds from the ZINC15 database—a task impossible for physical high-throughput methods—was accomplished in silico in just four days by the Stokes team, yielding 6,820 high-probability candidates and ultimately eight structurally novel antibacterial compounds .

Halicin and Abaucin: The First Fruits of Computational Discovery

No narrative of AI antibiotics would be complete without Halicin, the molecule that proved computers could find what human intuition missed. Structurally, Halicin is divergent from conventional antibiotics. Its nearest known antibiotic neighbor, metronidazole, shares only a Tanimoto similarity of ~0.21—a measure of structural

overlap where 1.0 represents identity . This divergence is not merely academic; it explains Halicin's ability to evade existing resistance mechanisms.

Halicin operates through an unusual mechanism: it disrupts the bacterial proton gradient by interfering with proton transport across the cell membrane, ultimately starving the bacterium of ATP . Because this mode of action differs fundamentally from beta-lactams, fluoroquinolones, or aminoglycosides, resistance mutations selected by traditional antibiotics do not protect bacteria against Halicin. In murine models, the compound effectively treated *Clostridioides difficile* and pan-resistant *A. baumannii* infections—demonstrating that in silico predictions could translate to in vivo efficacy .

Figure 3: Chemical structures of Halicin and ZINC000100032716, two AI-discovered antibiotics with novel scaffolds. (Image: Chemical & Engineering News)

If Halicin proved that AI could discover broad-spectrum agents, Abaucin—discovered in 2023—demonstrated the power of narrow-spectrum precision. *Acinetobacter baumannii*, a WHO-priority pathogen responsible for severe nosocomial infections with mortality rates approaching 43%, has developed resistance to virtually every last-resort antibiotic, including carbapenems . Using a machine-learning model trained on 7,500 known compounds, researchers screened 6,680 unknown molecules and identified 240 hits, of which nine displayed antibacterial activity. The most potent was Abaucin .

Unlike Halicin, Abaucin is exquisitely specific. It inhibits the lipoprotein-releasing system transmembrane protein LolE, disrupting lipoprotein trafficking exclusively in *A. baumannii* . Crucially, Abaucin showed no activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, or even commensal gut bacteria at concentrations 20 times its effective dose against *A. baumannii* . This narrow spectrum is a feature, not a bug. Broad-spectrum antibiotics exert universal selective pressure, driving resistance across diverse species and decimating the protective microbiome. A targeted

agent like Abaucin represents the holy grail of precision infectious disease medicine: eliminate the pathogen while preserving the ecosystem.

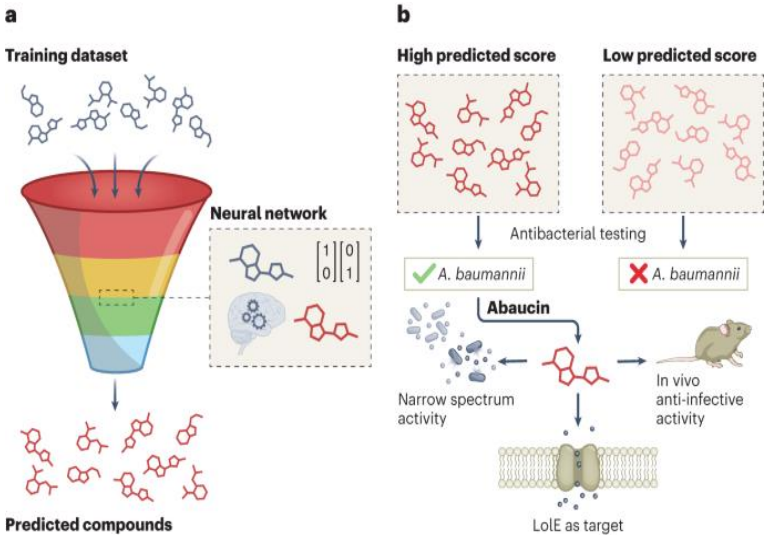

Figure 4: Deep learning workflow for antibiotic discovery, from training dataset curation to experimental validation. (Image: Nature Chemical Biology)

Mining Molecular De-Extinction and the ZINC15 Revolution

The success of Halicin and Abaucin opened floodgates. Researchers realized that AI could not only repurpose existing drugs but also mine entirely unexplored chemical territories. One of the most imaginative applications has been "molecular de-extinction"—the use of deep learning to resurrect antimicrobial peptides from extinct organisms.

In 2024, researchers developed APEX, a multitask deep learning model combining recurrent and attention neural networks to predict antimicrobial activity from peptide sequences . Trained on both proprietary and public datasets, APEX was deployed to mine the proteomes of extinct organisms—mammoths, giant elk, and ancient cattle—identifying encrypted peptides with antibiotic properties that evolution had tested and refined millions of years ago. The model achieved the highest Pearson correlation for minimum inhibitory concentration (MIC) prediction among all tested algorithms, validating its capacity to rank antimicrobial potency accurately .

Simultaneously, the scale of computational screening has reached staggering proportions. In 2024, machine learning-driven exploration of microbiomes analyzed 63,410 metagenomes and 87,920 prokaryotic genomes, yielding nearly one million prokaryotic peptide antibiotic sequences . This represents a paradigm shift: instead of

asking "what can we synthesize?" scientists now ask "what has nature already designed that we simply cannot see without AI?"

The ZINC15 database, containing approximately 1.5 billion virtual molecules, has become the proving ground for these algorithms. When Stokes et al. applied their retrained D-MPNN model to a focused subset of 107 million ZINC15 compounds, they identified two molecules—ZINC000100032716 and ZINC000225434673—with potent broad-spectrum activity that overcame common resistance determinants . The latter compound, with a Tanimoto similarity of only ~0.16 to its nearest known antibiotic, achieved complete sterilization of *E. coli* cultures within four hours . These discoveries underscore a critical insight: AI does not merely accelerate old discovery methods; it accesses genuinely novel chemical space.

Challenges, Limitations, and the Road Ahead

For all its promise, AI-driven antibiotic discovery is not a panacea. The field faces substantial hurdles that temper unbridled optimism. Foremost among these is the data problem. Machine learning models are fundamentally dependent on the quality, quantity, and diversity of their training data. Incomplete, biased, or poorly annotated datasets generate unreliable predictions—garbage in, garbage out . The antibacterial chemical space is still sparsely mapped; the 2,335 molecules used to train the original Halicin model represent a vanishingly small fraction of possible bioactive compounds. Validation remains the bottleneck. AI can identify promising candidates in silico within days, but the subsequent pipeline—synthesis, in vitro testing, in vivo animal models, and human clinical trials—still requires years and hundreds of millions of dollars . No algorithm can yet predict with perfect accuracy the complex pharmacokinetics, off-target toxicity, or manufacturing scalability of a novel molecule. The attrition rate for AI-discovered drugs in clinical phases remains to be determined, and early enthusiasm must be tempered by the historical reality that most promising preclinical compounds fail in humans.

Interpretability poses another challenge. Deep neural networks often function as "black boxes," providing predictions without mechanistic explanations. For regulatory agencies like the FDA and EMA, which increasingly demand mechanistic safety rationales, this opacity is problematic . Researchers are responding with attention-visualization techniques and surrogate modeling, but explainable AI in drug discovery remains a work in progress.

Table 2: Advantages and Limitations of AI in Antibiotic Development

Dimension	Advantages	Limitations
Speed	Screens billions of compounds in days; reduces early discovery from years to weeks	Clinical validation still requires years; no acceleration of Phase I-III trials
Cost	Decreases wet-lab screening expenses; prioritizes only high-probability candidates	High upfront investment in computational infrastructure and data curation
Novelty	Identifies structurally divergent scaffolds invisible to human chemists	Novel structures may face synthesis challenges or poor drug-like properties
Specificity	Enables narrow-spectrum design preserving microbiome (e.g., Abaucin)	Narrow targets may limit commercial viability and clinical utility
Resistance Evasion	Discovers compounds with unconventional mechanisms of action	Bacteria can still evolve de novo resistance under sufficient selective pressure
Data Requirements	Can generalize from modest training sets with transfer learning	Requires high-quality, standardized, and diverse biological data
Interpretability	Emerging tools for attention mapping and feature importance	Core models remain "black boxes," complicating regulatory approval

Ethical and economic considerations also loom. The global AI in drug discovery market, valued at approximately $19.89 billion in 2025 and projected to reach $160.49 billion by 2035 , is dominated by North American and European players. There is a risk that AI-discovered antibiotics, developed with massive private investment, will be priced beyond the reach of health systems in the very regions—South-East Asia, Africa, the Eastern Mediterranean—where resistance is most acute . Ensuring equitable access will require deliberate policy interventions, including advance market commitments, patent pools, and public-private partnerships.

The Market, the Clinic, and the Future Landscape

Despite these challenges, the trajectory is unmistakably upward. The AI drug discovery ecosystem has matured rapidly. By 2025, major players including Exscientia, Insilico Medicine, Recursion Pharmaceuticals, and Isomorphic Labs had advanced multiple AI-designed molecules into mid-stage clinical trials . NVIDIA's BioNeMo platform and open-source protein models like ESM-2 have democratized access to computational tools, enabling even resource-constrained biotechs to participate .
Generative AI represents the next frontier. Unlike discriminative models that simply classify existing compounds, generative models—diffusion models, transformers, and reinforcement learning agents—can design entirely new molecular architectures optimized for binding affinity, ADMET properties, and synthesizability . In 2024–2025, generative approaches produced six structurally novel molecules with validated antibacterial activity against *A. baumannii*, representing true de novo design rather than repurposing .

Autonomous laboratories are emerging as the physical manifestation of this digital revolution. Self-operating labs integrate AI-driven design with robotic synthesis and high-throughput testing in continuous design-build-test-learn (DBTL) cycles . These systems promise to compress the iteration loop from months to days, creating a virtuous cycle where each experiment refines the model, and each model prediction guides the next experiment.

Yet the ultimate measure of success will not be publications or patents, but lives saved. The WHO has emphasized that innovation must be paired with responsible antibiotic stewardship, robust surveillance, and universal access to diagnostics and quality-assured medicines . AI can discover the cure, but only health systems can ensure it reaches the patient.

Conclusion

The story of antibiotic discovery has come full circle—from Fleming's accidental mold to algorithms that deliberately design molecules with surgical precision. Artificial intelligence is not merely an incremental improvement to existing methods; it is a fundamental reordering of how we search for cures in chemical space. By training neural networks on modest datasets and unleashing them on libraries of billions, researchers have identified Halicin, Abaucin, and hundreds of other candidates that defy conventional discovery logic. These molecules are structurally novel, mechanistically unconventional, and in some cases, exquisitely targeted.

But the narrative of "Code, Cure, Repeat" carries a caveat. Code generates hypotheses; only rigorous experimental validation produces cures. And cures, however brilliant, mean little if they remain trapped behind paywalls or regulatory bottlenecks. The repetition we need is not just algorithmic iteration—it is the relentless, global commitment to translating digital discoveries into bedside treatments.

As antimicrobial resistance continues its upward trajectory, outpacing traditional drug development by an ever-widening margin, AI offers something precious: time. Time to out-evolve the superbugs. Time to rebuild the antibiotic pipeline. Time to ensure that the next century of medicine does not retreat into a pre-penicillin darkness. The algorithms have spoken. The molecules have been found. The task now falls to us—to synthesize, to test, to steward, and to deliver. Code has written the prescription. Whether society can fill it remains the defining medical challenge of our age.

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