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Mini Review

Targeting multidrug-resistant *Acinetobacter baumannii* with pyrazole therapeutics: The role of clinical microbiology and structure–activity relationship (SAR) insights

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Abstract

The escalating prevalence of multidrug-resistant (MDR) *Acinetobacter baumannii* presents a formidable challenge to global healthcare, necessitating innovative therapeutic strategies. This review explores the critical role of clinical microbiology in the detection, surveillance, and management of MDR *A. baumannii* infections, underscoring the importance of accurate diagnostics and infection control. Concurrently, the pyrazole heterocyclic scaffold emerges as a promising molecular framework in the development of novel antibacterial agents, owing to its versatile chemical properties and demonstrated bioactivity against resistant strains. MDR *A. baumannii* has emerged as a major global health threat, with prevalence rates exceeding 60% in many hospital-acquired infections, thereby underscoring the urgent need for novel therapeutic approaches. This review provides a comprehensive analysis of recent advances in the development of pyrazole-based scaffolds, emphasizing structure-activity relationship (SAR) insights that rational design and fine-tuning of antibacterial potency and target selectivity. This integrated perspective highlights the synergy between clinical microbiological approaches and medicinal chemistry advancements, contributing to the design of more effective antimicrobial agents against the increasingly resistant and clinically significant pathogen *A. baumannii*.

Introduction

The global healthcare community is increasingly imperiled by the rise of bacterial pathogens exhibiting multidrug resistance (MDR), posing an existential challenge to conventional antimicrobial therapy. Central to this crisis are the ESKAPE pathogens-*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter*-which are renowned for their ability to "escape" the effects of widely used antibiotics [1,2]. Of these, *A. baumannii* has emerged as one of the most formidable nosocomial threats, owing to its intrinsic and acquired resistance mechanisms that render standard treatment regimens increasingly ineffective. The modern era of clinical microbiology thus finds itself navigating a precarious post-antibiotic landscape in which even routine infections may escalate to life-threatening conditions [3,4].

From a microbiological point of view, Gram-negative pathogens of the ESKAPE group, particularly *A. baumannii*, present unprecedented therapeutic challenges due to their complex resistance mechanism. These bacteria possess efflux pump systems, a robust lipopolysaccharide-rich outer membrane, and a thin peptidoglycan layer (~5–10 nm), all of which confer considerable impermeability to antimicrobial agents [5,6]. In contrast, Gram-positive organisms, with a thicker peptidoglycan layer (~20–40 nm), allow for more facile antibiotic penetration and are therefore more susceptible to treatment [7,8].

Antimicrobial susceptibility data from the Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) surveillance studies conducted across 15 major medical centers in North America highlighted the deteriorating efficacy of critical antibiotics against *A. baumannii*, with resistance rates exceeding 40% for agents such as aztreonam, ceftazidime, gentamicin, meropenem, and imipenem [9]. Historically, the discovery of penicillin heralded the advent of heterocyclic-based antibiotics, with β-lactams targeting DD-transpeptidase enzymes involved in bacterial cell wall biosynthesis [10]. Nevertheless, the widespread emergence of β-lactamase-producing strains, notably penicillinases, has rendered many of these agents obsolete [11,12]. As antimicrobial resistance continues to advance, the renewed clinical deployment of legacy antibiotics such as polymyxins and colistins-cationic lipopeptides originally introduced in the 1950s has become paramount interest [13]. However, their therapeutic relevance remains limited due to significant nephrotoxicity and the alarming rise of colistin-resistant *A. baumannii* strains, thereby underscoring the urgent need for novel antimicrobial scaffolds [14]. In this context, pyrazole-based molecular models have garnered substantial attention as promising candidates for next-generation antibacterial agents. The pyrazole moiety is a privileged heterocyclic motif widely used in medicinal, synthetic, and bioorganic chemistry, owing to its tunable electronic properties, chemical versatility, and usual presence in bioactive compounds [15-18]. Numerous synthetic and natural products comprising pyrazole scaffolds (**Figure 1**) exhibit a broad spectrum of biological activity, including potent antibacterial effects.

Augmenting pharmacological development, clinical microbiology plays an indispensable role in the containment of MDR *A. baumannii* within hospital settings. The implementation of proactive surveillance measures to detect colonization by MDR or pandrug-resistant (PDR) strains can inform timely infection control responses. Nevertheless, current methodologies for detecting colonization lack sensitivity and standardization. Initial studies indicate that cultures obtained from sites such as the anterior nares, oropharynx, skin, and rectum-when grown on MacConkey agar enriched with ceftazidime (8 μg/mL) and amphotericin B (2 μg/mL)-yield detection rates as low as 25% per site [19]. These limitations emphasize the necessity for more robust diagnostic tools, such as molecular diagnostics, polymerase chain reaction (PCR)-based screening, and multiplexed pathogen panels, to accurately identify colonized individuals and prevent nosocomial dissemination [11,14,15–17]. Furthermore, the impact of such surveillance on clinical outcomes including infection incidence and transmission dynamics remains insufficiently characterized. Future investigations must not only refine the sensitivity and specificity of detection platforms but also rigorously evaluate their integration into infection control protocols and antimicrobial stewardship frameworks. In summary, an integrated strategy combining structure-activity relationship (SAR)-driven development of pyrazole therapeutics with enhanced clinical microbiology surveillance is critical to confronting the escalating threat posed by MDR *A. baumannii*. Through interdisciplinary alliance, the prospects of restoring effective antibacterial therapy and mitigating the global spread of this resilient pathogen can be meaningfully advanced. While numerous studies have demonstrated the promising pharmacological efficacy of pyrazole-based compounds, notably in antimicrobial and anticancer contexts, their pharmacokinetic properties and toxicological profiles remain underexplored. This gap limits the ability to assess their clinical viability. Comprehensive evaluation of absorption, distribution, metabolism, excretion (ADME), and safety are essential for advancing these compounds from preclinical findings to therapeutic application. Future studies should prioritize these aspects to better define the translational potential of pyrazole derivatives. This review aims to underscore the pivotal role of clinical microbiology insights with detailed structure–activity relationship (SAR) studies in advancing pyrazole-based therapeutic targeting multidrug-resistant *A. baumannii*. By elucidating these aspects, the review seeks to advance understanding and foster innovative strategies to combat this highly resilient pathogen, ultimately contributing to the development of more effective and precise antimicrobial interventions.

Chemically Diversified Pyrazole Scaffolds as Promising Therapeutics for Multidrug-Resistant *Acinetobacter baumannii*

Thiophene-functionalized pyrazolo [1,5-a]pyrimidines (compounds **1**; Minimum Inhibitory Concentration (MIC): 31.25–250 μg/mL; **Figure 2**) demonstrated limited to moderate bactericidal activity against *Acinetobacter baumannii*. SAR elucidation revealed that halogenation of the phenyl ring significantly augmented activity, whereas aryl substitution at the C-3 amino position exerted negligible influence [20]. Replacing the pyrazole ring with 1,2,4- or 1,2,3-triazoles did not improve antibacterial efficacy [21,22]. Enhanced antibacterial performance was further observed with aminophenyl and arylazo substituents due to increase in the electron density and more solubility. Most derivatives displayed minimal activity against *P. aeruginosa* and Gram-positive strains, except **1a**

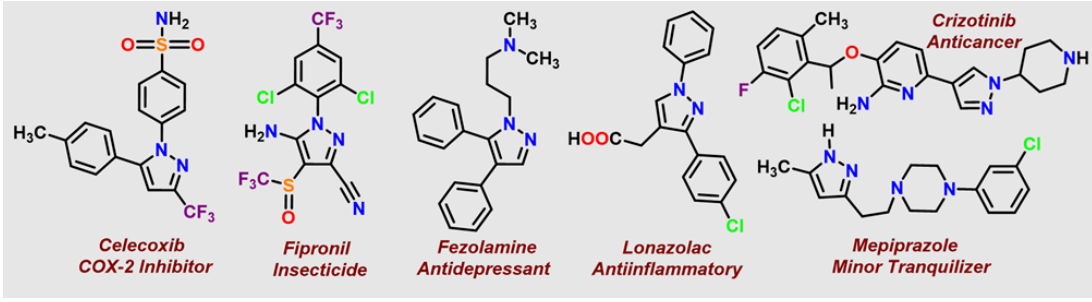

Figure 1. Structurally important pyrazole-derived therapeutic agents.

(**Figure 5**), which retained efficacy against *S. aureus* and *S. mutans*. The substitution of electron-withdrawing groups, significantly enhanced potency, outperforming standard antibiotics in *E. coli*, *K. pneumoniae*, and *A. baumannii*.

In 2022, Sannio *et al* [23]. investigated pyrazole carboxamides, previously reported by Mugnaini *et al* [24], for antibacterial activity. While one compound showed pronounced activity against Gram-positive strains, derivatives **2** and **3** in **Figure 2** retained activity against Gram-negative bacteria, excluding *P. aeruginosa*. Compound **2 (Figure 2)** had a narrower spectrum with enhanced cytotoxicity toward eukaryotic membranes, whereas **3 (Figure 2)** exhibited synergism with colistin and potentiated bactericidal activity against colistin-resistant *A. baumannii*, most likely due to membrane-disrupting interactions.

Pyrazole-imine hybrids (**4, Figure 2)** exhibited the notable bacteriostatic activity (MIC: 1.56–12.5 µg/mL), with halogenated aromatics outperforming other derivatives. Replacing trifluoromethyl groups with carboxylic acids significantly improved potency (MIC: 0.78–3.12 µg/mL). A pyrazole–penicillin hybrid restored imipenem efficacy against carbapenem-resistant *A. baumannii* strains [25,26].

Pyrazole hydrazones (MIC 4 µg/mL) exhibited strong anti-*A. baumannii* properties without cytotoxicity. Further optimization led to compound **5** (**Figure 3**, MIC: 0.73 µg/mL), with analogs also targeting *S. aureus* and *B. subtilis* [27]. Structural modifications such as fluorine-to-carboxylic acid preserved the antibacterial activity, while coumarin substitutions **(6, Figure 3)** attenuated activity [28].

Host-directed therapy has also shown promise. Inhibition of the small GTPase ARF6-via genetic ablation or pharmacological blockade-improved survival in murine *A. baumannii* pneumonia models. Small-molecule inhibitors **(7, Figure 3)** restored endothelial barrier integrity by disrupting LPS-induced TLR4/MyD88/ARF6 signaling, offering a novel adjunctive strategy against resistant Gram-negative infections [29,30].

In 2020, Mugnaini *et al* [24]. evaluated various compounds for antibacterial efficiency, identifying only 54% compounds with measurable inhibitor activity (≥4 mm inhibition zone), particularly against Gram-negative ESKAPE pathogens [31] such as *K. pneumoniae* and *A. baumannii*. Only a few compounds exhibited potent inhibition (≥10 mm), with ethyl ester derivatives demonstrating superior activity. Whitt *et al.* [32,33] synthesized a library of fluorinated pyrazole-hydrazones (**8a–8d**, **Figure 3**), leveraging the metabolic stability of C–F bonds. These analogs were screened against seven Gram-negative strains. While most exhibited limited spectrum, derivatives bearing 3- or 4-fluorophenyl moieties showed modest activity against *A. baumannii*, with the most active compound achieving a MIC of 3.125 µg/mL [34].

In 2022, Ali Mohamed and Ammar [35] synthesized pyrazole derivatives containing thiazol-4-one/thiophene scaffolds, demonstrating potent antibacterial activity with minimum inhibitory concentrations (MICs) as low as 0.78 µg/mL. These compounds exhibited low hemolytic activity and significant inhibition of DNA gyrase and dihydrofolate reductase (DHFR), with favorable docking

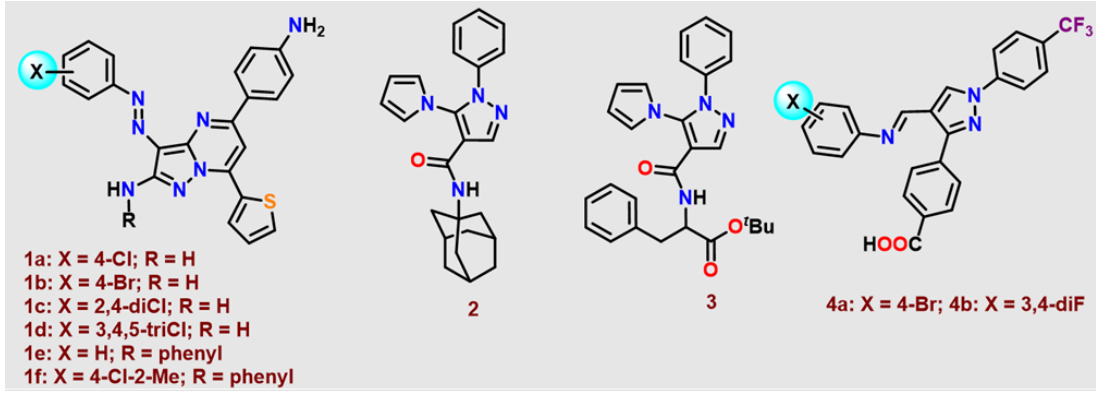

Figure 2. Di-, tri, and tetra-substituted pyrazole derivatives (MIC: 1.56–250 µg/mL) as antibacterials against *A. baumannii.*

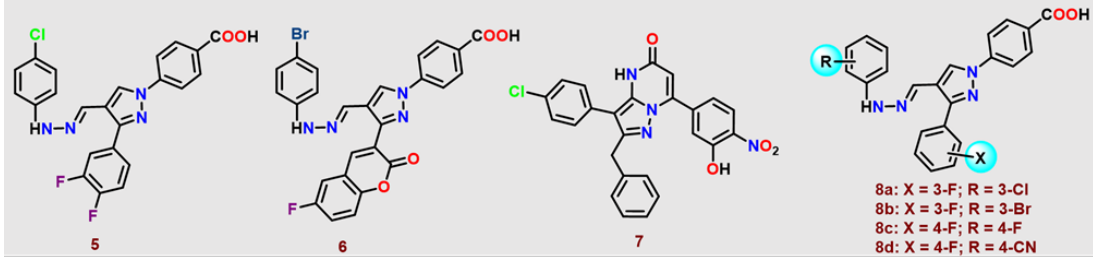

Figure 3. Hydrazone-functionalized pyrazole derivatives (**5** and **6**; MIC: 0.73–6.25 µg/mL) as potential anti-*A. baumannii* agents and diversified pyrazoles (**7** and **8**; MIC: 0.31–3.125 µg/mL) as antibacterial agents.

scores indicating strong binding affinities. Earlier in 2021, Ahmad *et al.* [36]. developed pyrazole benzamide derivatives, notably compound **12b** (**Figure 4**), which displayed superior activity against NDM-1-positive *A. baumannii*. Molecular docking studies revealed stable binding conformations, supporting the compounds' potential as therapeutic agents. In the past, Whitt *et al.* [32,33]. synthesized pyrazole hydrazone derivatives, identifying compounds **8** (**Figure 3**) with MICs ranging from 3.125 to 6.25 µg/mL against *A. baumannii*. These derivatives exhibited selective activity against Gram-negative bacteria, with limited efficacy against other strains.

Alfei *et al.* [37]. used pyrazole derivative CB1H into cationic copolymer matrices resulted in CB1H-copolymer nanoparticles, which exhibited potent antibacterial activity against various clinical isolates, including both Gram-positive and Gram-negative MDR strains. Minimum inhibitory concentrations (MICs) ranged from 0.6 to 4.M, demonstrating up to a 16.4-fold improvement over unmodified CB1H. Time-kill assays confirmed rapid bactericidal effects, with over a 4-log reduction in bacterial counts within 4 hours for *Escherichia coli* and *Klebsiella pneumoniae*, and complete eradication of *Pseudomonas aeruginosa* within 1 hour. Cytotoxicity evaluations on human keratinocyte cells (HaCaT) indicated selectivity indices up to 2.4, suggesting favorable therapeutic profiles [38].-

The synthesis of CR232 (13, **Figure 4**), a pyrazole derivative with limited solubility, into dendrimer-based G5K nanoparticles (NPs) addressed solubility challenges and enhanced antimicrobial potency. CR232-G5K NPs demonstrated MICs ranging from 0.36 to 2.89 µM against various MDR strains, including colistin-resistant *P. aeruginosa* and carbapenemase-producing *K. pneumoniae*. Time-kill studies revealed rapid bactericidal activity, with no significant bacterial regrowth after 24 hours. Cytotoxicity assessments on HaCaT cells indicated selectivity indices between 34.5 and 276.4, underscoring the safety and efficacy of the formulation [37,39].

In 2018, Hassan *et al.* [40]. evaluated the *in vitro* antimicrobial efficacy of fused pyrazoles (15–17**, Figure 5**), Schiff bases (18**, Figure 5**), and 5-aminopyrazoles (19, **Figure 5**) against multidrug-resistant bacterial strains (MDRB) (**Figure 5**). Compounds **15a** and Schiff base **18c** in **Figure 5** exhibited pronounced potency against *S. aureus* (MIC: 7.81 µg/mL). For *S. epidermidis*, **15b** (1.95 µg/mL), **17a** (0.97 µg/mL), and **18c** (3.91 µg/mL) demonstrated significant activity (**Figure 5**). Compounds **15b**, **16**, and **17a,b** (**Figure 5**) (3.91 µg/mL) displayed unprecedented efficacy against *E. faecalis*. Compounds **19a** and **19b** (**Figure 5**) demonstrated potent inhibitory activity against *A. baumannii*, with MIC values of 3.91 µg/mL. In contrast, compounds **15a, 15c, 16,** and **18** (**Figure 5**) exhibited moderate antibacterial activity, each with MIC values of 7.81 µg/mL. Against *E. cloacae*, compounds **16** (1.95 µg/mL), **17a** (0.48 µg/mL), and **18a** (3.91 µg/mL) (**Figure 5**) showed significant efficacy. Additionally, compounds **17a** and **17b** displayed moderate inhibition of *E. coli*, each with an MIC of 7.81 µg/mL. Subsequent screening of pyrazole derivatives (**20**, **Figure 5**) revealed the primarily bacteriostatic effects against *A. baumannii*. Fluoro-substituted congeners (**20a,b, Figure 5**) uniformly inhibited all tested strains (MIC 6.25 µg/mL), whereas chloro-substituted (**20c, Figure 5**) exhibited enhanced potency against Ab06 (3.125 µg/mL). The 4-bromophenyl analog (**20e, Figure 5**) demonstrated superior inhibition (MIC 1.56 µg/mL) against Ab06, with other analogs exhibiting attenuated or moderate efficacy.

Recently, Braun-Cornejo *et al.* [41]. synthesized a library of eNTRy-rule-compliant derivatives by introducing ionizable nitrogen moieties into a planar, rigid pyrazole-amide scaffold (**21–27**, **Figure 6**), thereby enhancing Gram-negative permeability.

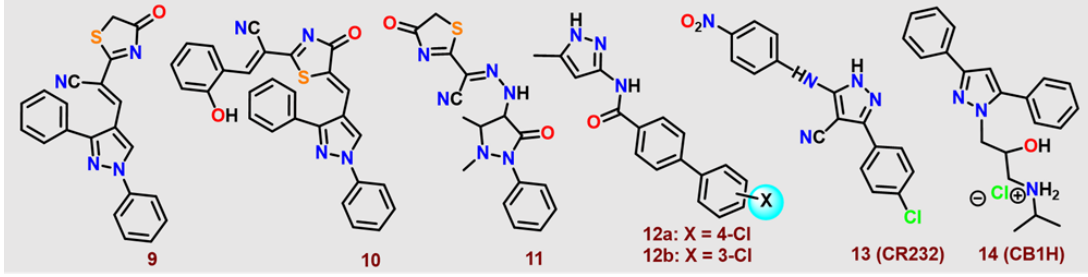

Figure 4. Heterocyclic conjugated pyrazoles (**9-11**; MIC: 0.97–12.5 µg/mL), pyrazole benzamide derivatives (**12**; MIC: 0.73–6.25 µg/mL), and other pyrazoles (**13-CR232**; MIC: 0.6–4.8µg/mL and **14-CB1H**; MIC: 0.72–1.44µg/mL) as anti-*A. baumannii* agents.

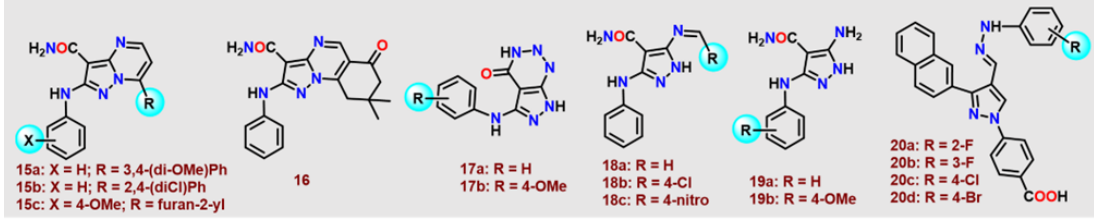

Figure 5. Polysubstituted pyrazole derivatives (**15-20**; MIC: 1.56–7.81µg/mL) as antibacterial agents against *A. baumannii.*

Various derivatives (**21–27**, **Figure 6**) displayed moderate to robust antibacterial activity against *A. baumannii* (≥45% inhibition at 50 µM; MIC95 <25 µM), with **25** and **27** in **Figure 6** achieving MIC95 values of 22 and 17 µM, respectively. Their analogous potency against *E. coli* K12 suggests conserved bioavailability and target engagement. Abu-Zaied *et al* [42]. also used acrylamide-pyrazole conjugates, compound (**28a, Figure 6**) which exhibited an inhibition zone of 18 ± 1 mm against *A. baumannii*, closely rivaled by (**28b**, **Figure 6**) (21±1 mm), relative to Tigecycline (23±0.4 mm).

Pyrazole-based scaffolds have emerged as a promising chemotype in the development of novel antibacterial agents, particularly against multidrug-resistant *A. baumannii*. A comprehensive evaluation of diverse pyrazole derivatives has revealed significant antibacterial potential, driven by specific structural modifications that enhance activity and selectivity. The variations in the pyrazole scaffold-such as halogen substitution, heterocyclic fusion, and hybridization with other pharmacophores-play a critical role in modulating antimicrobial efficacy as shown in **Table 1**. These modifications not

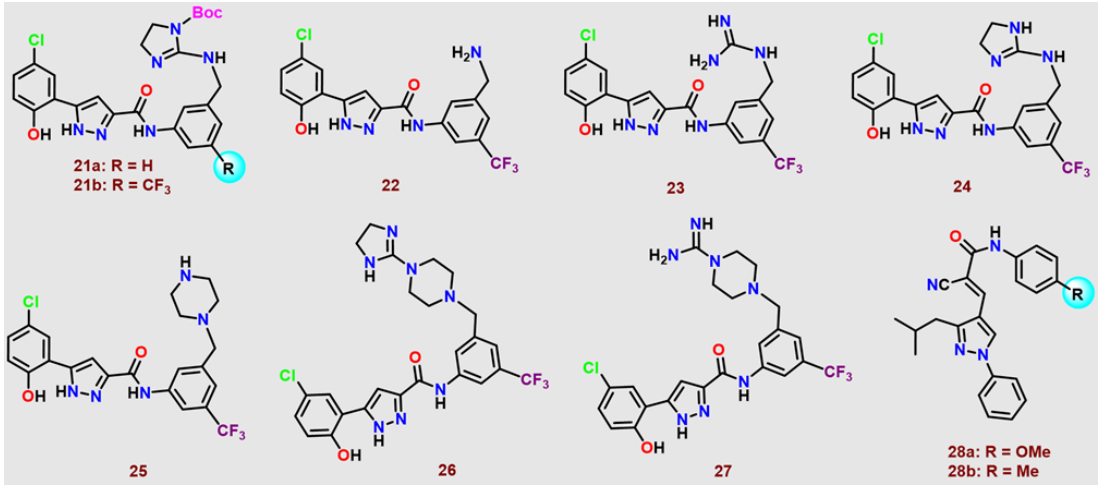

Figure 6. Polysubstituted pyrazoles functionalized with amines/N-alkylated guanidines (**21-27**) and conjugated acrylamide pyrazoles (**28**): A promising candidate against *A. baumannii* infections.

Table 1. Summary of pyrazole derivatives active against *A. baumannii*.

Compound No.	Modification/Type	MIC (µg/mL)	Observed Effect
1	Thiophene–pyrazolo[1,5-a]pyrimidines	31.25–250	Halogenated phenyl ring enhanced activity; some equal to tigecycline
2	Pyrazole carboxamide analog	Moderate	Narrow spectrum; enhanced membrane damage
3	Pyrazole carboxamide analog	Moderate	Synergy with colistin; activity against colistin-resistant strains
4	Pyrazole-imine hybrids with halogenated aryl rings	1.56–6.25	Comparable to colistin; disrupt membrane integrity
5	Pyrazole hydrazones	0.73–4	Active against *A. baumannii*; non-toxic to HEK cells
6	Fluorinated/coumarin-modified pyrazoles	0.78–6.25	Activity depends on substitution; coumarins reduced efficacy
7	ARF6 inhibitors (vascular targeting)	0.31	Effective in vivo by restoring host vasculature during infection
8	Fluorinated pyrazole hydrazones	3.125	Mild to moderate activity
9–11	Thiazol-4-one/thiophene hybrids	0.97–12.5	Dual enzyme inhibition (DNA gyrase, DHFR); biofilm inhibition
12	Benzamide derivatives (via Suzuki coupling)	0.73–6.25	12b most active; docking confirmed binding to NDM-1 enzyme
13 (CB1H)	Nanoparticle-encapsulated pyrazole	0.6–4.8	Strong effect vs. MDR strains; enhanced selectivity indices (SIs)
14 (CR232)	Dendrimer-based pyrazole formulation	0.72–1.44	Effective vs. colistin-resistant strains; high SI and fast bactericidal effect
15	Fused pyrazole derivative	3.91–7.81	Moderate to Good efficacy vs. *A. baumannii*

16	Schiff base pyrazole	7.81	Good activity vs. *A. baumannii*, *E. faecalis*
17	5-Aminopyrazole	3.91–7.81	Strong activity against *S. epidermidis*, *E. cloacae*, and *A. baumannii*
18	Schiff bases	7.81	Moderate effect vs. *A. baumannii*
19	5-Aminopyrazoles	3.91	Strong activity; best among Schiff base and 5-aminopyrazoles
20	Fluoro-/chloro-/bromo-substituted pyrazoles	1.56–6.25	Specific strains inhibited; 20d most potent (1.56 μg/mL)
21–27	Pyrazole-amides modified to follow eNTRy rules	17–22 μM (MIC_{95})	25 and 27: Best hits; good activity in *A. baumannii* and E. coli
28a	Acrylamide–pyrazole conjugate	Zone: 18±1 mm	Moderate inhibition; tested by zone of inhibition assay
28b	Acrylamide–pyrazole conjugate	Zone: 21±1 mm	Stronger than 28a; comparable to tigecycline (23±0.4 mm)

only improve membrane permeability but also reduce recognition by bacterial efflux pumps and enhance intracellular target engagement. Consequently, pyrazole-based compounds can potentially overcome resistance mechanisms such as porin loss and efflux pump activity, which are frequently observed in MDR *A. baumannii*. Beyond the conventional antibacterial action, the strategic design of pyrazole derivatives can also exploit vulnerabilities in bacterial virulence mechanisms. Key virulence factors in *A. baumannii*, such as outer membrane proteins (OMPs) like OmpA and CarO, contribute significantly to host cell adhesion, immune evasion, and antibiotic resistance. Inhibiting these targets with small molecules may impair bacterial survival and enhance susceptibility to existing antibiotics. Similarly, the quorum sensing (QS) system-which governs biofilm formation, surface motility, and expression of virulence genes-represents another attractive target. Pyrazole scaffolds, owing to their structural adaptability and physicochemical versatility, are particularly well-suited for optimization against such non-traditional targets. Incorporating SAR insights not only from bactericidal activity but also from anti-virulence effects may result next-generation therapeutics that disarm the pathogen without exerting direct selective pressure, thus offering a complementary strategy to traditional antibiotics in the fight against MDR *A. baumannii*.

However, despite promising *in vitro* efficacy, the translation of pyrazole-based compounds into viable clinical candidates requires a series of rigorous steps. The development process typically begins with SAR-driven lead optimization to improve potency, selectivity, and safety profiles. *In silico* ADMET (absorption, distribution, metabolism, excretion, and toxicity) predictions are employed to identify pharmacologically viable compounds. Subsequently, *in vivo* studies in relevant infection models assess pharmacokinetics, tissue distribution, therapeutic efficacy, and systemic toxicity. Given the challenges associated with solubility and bioavailability, advanced drug delivery strategies-such as nanoparticle encapsulation, liposomal formulations, or prodrug design-are often necessary to enhance therapeutic potential.

Prior to entering clinical trials, candidate compounds must pass regulatory preclinical safety assessments, including genotoxicity and organ-specific toxicity studies under good laboratory practice conditions. Those meeting safety and efficacy benchmarks can proceed through the clinical development pipeline, beginning with Phase I trials (focused on safety and tolerability in healthy volunteers), followed by Phase II (dose optimization and preliminary efficacy in patients), and Phase III (large-scale validation of clinical benefit). For *A. baumannii* infections-especially in critically ill patients-clinical trials must also consider infection complexity, host immune status, and the potential for resistance evolution. In many cases, combination therapy approaches may be evaluated to enhance efficacy and reduce the likelihood of resistance development.

Clinical Significance and Impact of *Acinetobacter Baumannii* Infections

Acinetobacter baumannii exhibits a notorious propensity to colonize and infect critically ill patients, who inherently possess poor prognoses irrespective of secondary infections, complicating the precise elucidation of its clinical impact and fueling persistent controversy within the literature [43–45]. Pronounced methodological heterogeneity across studies further obfuscates definitive conclusions [19]. Although most investigations employ matched cohort or case-control frameworks, heterogeneity in case definitions and control group criteria is pervasive. Case definitions variably encompass patients with *A. baumannii* infection alone, combined infection and colonization, single- versus multi-site infections and inclusion of polymicrobial infections. Controls range from uninfected and uncolonized individuals, colonized but uninfected subjects, infection with susceptible isolates only, to infection with any pathogen regardless of specificity. Additionally, inconsistency in severity-of-illness adjustments, comorbidity matching, and species identification methods further undermines outcome reliability. In recent studies, the molecular diagnostics are increasingly relevant for tackling multidrug-resistant *Acinetobacter baumannii* and directly support the discovery of new agents such as pyrazole derivatives. Whole-genome sequencing (WGS) has been used to map hospital transmission events, uncover novel resistance genes, and characterize colistin-resistant strains, thereby providing critical insights into resistance mechanisms [46]. In parallel, rapid PCR-based diagnostics enable same-day identification of pathogens and resistance determinants, facilitating faster clinical decision-making process [47]. The integration of these tools with medicinal chemistry enhances drug discovery by ensuring that new scaffolds, including pyrazoles, are evaluated against genetically defined, clinically relevant isolates. Because pyrazoles can be readily modified to tune their antibacterial activity, aligning SAR data with resistance profiles identified by WGS and PCR accelerates rational design and increases the translational potential of these compounds.

A notable CDC analysis incorporating rigorous confounder adjustment and strict case-control criteria reported no statistically significant increase in mortality among patients with multidrug-resistant *A. baumannii* compared to uninfected controls (OR 6.6; 95% CI: 0.4–108.3), though prolonged hospital and ICU stays were observed [45]. These findings are consistent with select studies [48,49] but contrast with others linking multidrug or carbapenem resistance to worse outcomes [50–53]. Complementary analyses further suggest that *A. baumannii* bacteremia may confer higher mortality risk than bacteremia due to other Gram-negative pathogens, including *Klebsiella pneumonia* [54,55]. Kaplan–Meier analyses have also shown increased mortality in cases of multidrug-resistant *A. baumannii* compared to multidrug-resistant *Pseudomonas aeruginosa* [56]. However, these studies often lack standardized severity scoring systems (e.g., APACHE, McCabe, Charlson indices), which may account for conflicting results across the literature.

Geographic clustering of studies raises the possibility that strain-specific virulence contributes to the observed variability in clinical outcomes, a hypothesis supported by disproportionately severe presentations of community-acquired *A. baumannii* infections in tropical regions [57]. The role of empirical antimicrobial therapy remains similarly contentious: while some studies identify inappropriate initial therapy as an independent predictor of mortality [58,59], others do not [60,61], likely reflecting sample size limitations and insufficient statistical power.

Comparative data between *A. baumannii* and non-*baumannii Acinetobacter* species are limited. A Korean cohort study observed no significant mortality difference after adjustment, although *A. baumannii* was associated with prolonged hospitalization [62]. Nonetheless, limitations in species identification undermine confidence in such findings. Mounting genomic evidence challenges the long-held view of *A. baumannii* as a low-virulence organism, revealing ongoing acquisition of multidrug resistance and putative virulence factors [63]. These evolutionary adaptations underscore the emergence of a more formidable pathogen with escalating implications for therapeutic efficacy and clinical management.

Host-pathogen Dynamics Involving *Acinetobacter*

Relative to other Gram-negative pathogens such as *Pseudomonas aeruginosa*, the host-pathogen dynamics of *A. baumannii* remain scarce. Recent whole-genome sequencing has revealed an extensive arsenal of antibiotic resistance genes coupled with numerous pathogenicity islands within *A. baumannii* [63]. Intriguingly, many resistance determinants targeting antibiotics, heavy metals, and antiseptics appear horizontally acquired from highly virulent bacteria like *Pseudomonas*, *Salmonella*, and *Escherichia coli*, suggesting a parallel potential for the horizontal transfer of virulence factors [63].

Random mutagenesis studies in *A. baumannii* American Type Culture Collection (ATCC-17978) identified mutants with attenuated virulence localized to six pathogenicity islands, encoding transcriptional regulators, multidrug efflux pumps, and urease, although these phenotypes were characterized only in non-mammalian models [64]. Comparative genomics with the non-pathogenic *A. baylyi* revealed various unique gene clusters in *A. baumannii*, many of which are implicated in virulence, including 133-kb island harboring type IV secretion system homologs akin to those in *Legionella* and *Coxiella*. Additional virulence-related genes encode cell envelope components, pilus biogenesis machinery, and iron acquisition systems [64].

Focused studies have illuminated critical virulence mechanisms, including siderophore-mediated iron sequestration [65,66], biofilm formation [67], adherence via outer membrane proteins [68] (OMPs), and the immunostimulatory role of lipopolysaccharide [69] (LPS). To circumvent host-imposed iron limitation, *A. baumannii* secretes structurally diverse low-molecular-weight siderophores [65,66] whose expression exhibits pronounced strain variability and shares homology with siderophores from aquatic pathogens [66] such as *Vibrio anguillarum*. Its proclivity for biofilm formation on abiotic surfaces-aided by exopolysaccharide synthesis and type I pili encoded by the *csu* operon homologous to chaperone-usher pilus systems underpins its resilience in nosocomial environments [67]. Adherence to human bronchial epithelial cells and erythrocytes is mediated by pilus-like appendages, with notable clonal variation, including heightened adhesion among European clone II strains [68]. Subsequently, *A. baumannii* induces apoptosis via Omp38, an OMP targeting mitochondria and triggering both caspase-dependent and independent apoptotic cascades, though partial attenuation in Omp38 mutants suggests auxiliary cytotoxic effectors [70]. Moreover, *A. baumannii* harbors up to four quorum-sensing systems orchestrating diverse virulence gene expression, underscoring the sophistication of its regulatory networks.

Infection Control Perspective: The Persistence of *Acinetobacter Baumannii* as a Nosocomial/Hospital Pathogen

A. baumannii's tenacity as a nosocomial pathogen is underpinned by a triad of critical factors: pervasive multidrug resistance, extraordinary desiccation resilience, and partial tolerance to commonly employed disinfectants [71,72]. Epidemic strains exhibit elevated resistance profiles, particularly against fluoroquinolones and carbapenems, granting them a pronounced selective advantage in antimicrobial-saturated environments such as intensive care units [72]. This selective pressure fosters the persistence and clonal expansion of multidrug-resistant lineages over prolonged periods [72]. Furthermore, *A. baumannii* demonstrates an exceptional capacity to survive desiccation, with average survival times on dry surfaces approaching a month, markedly surpassing that of many other gram-negative bacteria. This prolonged viability on fomites and inanimate surfaces significantly contributes to its environmental persistence and facilitates indirect transmission within healthcare settings.

Although comprehensive resistance to disinfectants has not been conclusively established as a primary driver of outbreaks, suboptimal disinfection practices such as insufficient contact times or diluted biocide concentrations, may enable survival of viable bacteria, thus promoting nosocomial dissemination [71,72]. Current evidence suggests that minor procedural lapses rather than intrinsic biocide resistance are responsible for persistence post-cleaning. These intertwined factors multidrug resistance, desiccation endurance, and adaptive tolerance to disinfection synergistically fortify *A. baumannii*'s ability to persist and propagate in clinical environments, posing significant challenges to infection control and outbreak mitigation [19,71,72]. Despite the growing threat posed by multidrug-resistant *A. baumannii*, routine diagnostic methods in clinical microbiology laboratories often lag behind technological advances. Traditional culture-based identification, although reliable, is time-consuming and lacks resolution in differentiating between closely related *Acinetobacter* species, which can lead to diagnostic ambiguity and delayed treatment decisions.

In recent years, several modern tools have enhanced diagnostic precision and turnaround time. Matrix-Assisted Laser Desorption Ionization–Time of Flight Mass Spectrometry (MALDI-TOF MS) has become a cornerstone in clinical microbiology for rapid species-level identification of *A. baumannii*. This technology offers high-throughput, accurate, and cost-effective identification within minutes, significantly reducing diagnostic delays. However, its ability to distinguish *A. baumannii* from other members of the *A. calcoaceticus- A. baumannii* complex remains limited without additional confirmatory testing. Next-generation sequencing (NGS) has also emerged as a powerful tool, particularly for outbreak investigations, antimicrobial resistance gene profiling, and high-resolution strain typing. Whole genome sequencing enables precise phylogenetic analysis, identification of resistance determinants, and epidemiological tracking of MDR clones in healthcare settings. Although NGS is not yet routine in most diagnostic laboratories due to cost, infrastructure, and turnaround time, its clinical utility is increasingly recognized. In contrast, metagenomic sequencing approaches have the potential to identify pathogens and resistance mechanisms directly from clinical specimens, bypassing culture altogether. Integrating these advanced diagnostics into routine clinical practice would not only enhance pathogen detection and resistance profiling but also inform more targeted therapeutic interventions and infection control strategies which could be the key elements in managing MDR *A. baumannii* infections effectively.

Conclusions

In light of the escalating threat posed by MDR *Acinetobacter baumannii*, the development of novel therapeutic strategies has become an urgent priority in clinical microbiology and pharmaceutical research. This review highlights the structural versatility and pharmacodynamic adaptability of pyrazole derivatives as promising antimicrobial candidates, capable of circumventing conventional resistance mechanisms. Pyrazoles exhibit notable structural versatility, which facilitates targeted modifications to enhance bioactivity, selectivity, and pharmacological profiles. Integrating structure–activity relationship (SAR) insights with microbiological data enables rational design of potent analogs with improved efficacy against resistant strains. Moreover, understanding microbiological perspective and molecular interactions at the pathogen interface particularly with regard to membrane permeability, efflux evasion, and target engagement offers critical advantages in guiding compound optimization. While initial *in vitro* and preliminary *in silico* studies underscore the efficacy of various pyrazole derivatives, translation into clinical utility demands further *in vivo* validation and comprehensive toxicological assessments. Thus, the adaptability of pyrazole derivatives positions them as strategic candidates for hybrid drug design and combinatorial regimens aimed at overcoming complex resistance mechanisms. The rigorous *in vivo* validation establishes their clinical relevance, while solubility optimization overcomes the limitations associated poor aqueous solubility that often hinder oral absorption and systemic availability. Likewise, nanoparticle-based formulations can protect the drug from premature degradation, enhance controlled release, and improve tissue targeting, thereby maximizing bioavailability and therapeutic efficacy. Further, by integrating SAR-driven therapeutic discovery with modern diagnostic capabilities offers a promising path forward in combating *A. baumannii*. As rapid diagnostic platforms-such as MALDI-TOF MS, PCR panels, and next-generation sequencing-enable timely species identification and resistance profiling, they can be leveraged to guide the clinical deployment of rationally designed pyrazole derivatives. SAR data not only inform lead optimization but also allow for targeted therapeutic design against resistance mechanisms identified through molecular diagnostics. Embedding SAR-guided molecules within diagnostic-informed treatment algorithms could facilitate precision therapy, reduce empirical antibiotic use, and improve patient outcomes. The synergistic integration of medicinal chemistry, advanced microbiological diagnostics, and computational biology is crucial for advancing pyrazole-based therapeutics as potent and reliable agents in the emerging post-antimicrobial era.

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Conflicts of Interest

There is no conflict of interest.

Data Availability Statement

The literature search was conducted using PubMed, Web of Science, and Scopus. Data sharing is not applicable to this study, as no new data were generated or analyzed.

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