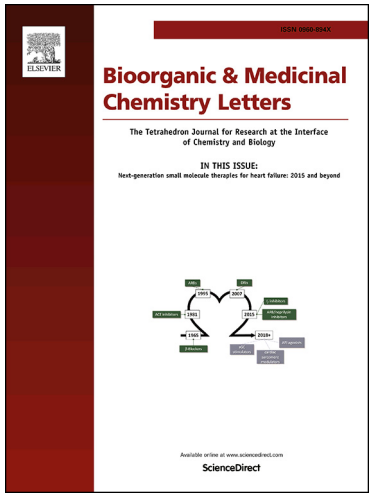
# Accepted Manuscript




Synthesis and Antimicrobial Studies of Hydrazone Derivatives of 4-[3-(2,4-difluorophenyl)-4-formyl-1*H*-pyrazol-1-yl]benzoic acid and 4-[3-(3,4-difluorophenyl)-4-formyl-1*H*-pyrazol-1-yl]benzoic acid

A.A. Zakeyah, J. Whitt, C. Duke, D.F. Gilmore, D.G. Meeker, M.S. Smeltzer, M.A. Alam

PII: S0960-894X(18)30578-X
DOI: https://doi.org/10.1016/j.bmcl.2018.07.016
Reference: BMCL 25947

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 21 May 2018
Revised Date: 3 July 2018
Accepted Date: 9 July 2018

Please cite this article as: Zakeyah, A.A., Whitt, J., Duke, C., Gilmore, D.F., Meeker, D.G., Smeltzer, M.S., Alam, M.A., Synthesis and Antimicrobial Studies of Hydrazone Derivatives of 4-[3-(2,4-difluorophenyl)-4-formyl-1*H*-pyrazol-1-yl]benzoic acid and 4-[3-(3,4-difluorophenyl)-4-formyl-1*H*-pyrazol-1-yl]benzoic acid, *Bioorganic & Medicinal Chemistry Letters* (2018), doi: https://doi.org/10.1016/j.bmcl.2018.07.016

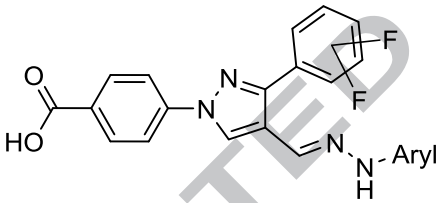
# Synthesis and Antimicrobial Studies of Hydrazone Derivatives of 4-[3-(2,4-difluorophenyl)-4-formyl-1*H*-pyrazol-1-yl]benzoic acid and 4-[3-(3,4-difluorophenyl)-4-formyl-1*H*-pyrazol-1-yl]benzoic acid

Zakeyah,[a] A. A.; Whitt,[a] J.; Duke,[a] C.; Gilmore,[b] D. F.; Meeker,[c] D. G.; Smeltzer,[c] M. S.; Alam*[a], M. A.
✉ Mohammad A. Alam
malam@astate.edu

[a] Department of Chemistry and Physics, College of Science and Mathematics, Arkansas State University, Jonesboro, AR 72467
[b] Department of Biological Sciences, College of Science and Mathematics, Arkansas State University, Jonesboro, AR 72467
[c] Department of Microbiology and Immunology, College of Medicine, University of Arkansas for Medical Sciences, 4301 W. Markham St., Little Rock, AR 72205

**Keywords**: Antimicrobial, Pyrazole, Hydrazone, Acinetobacter baumannii, and MRSA.
Declarations of interest: none

**Abstract**
Microbial resistance to antibiotics is an unresolved global concern, which needs urgent and coordinated action. One of the guidelines of the Centers for Disease Control and Preventions (CDC) to combat antibiotic resistance is the development of new antibiotics to treat drug-resistant bacteria. In our effort to find new antibiotics, we report the synthesis and antimicrobial studies of 30 new pyrazole derivatives. These novel molecules have been synthesized by using readily available starting materials and benign reaction conditions. Some of these molecules have shown activity with MIC values as low as 0.78 microgram/mL against four bacterial strains; *Staphylococcus aureus*, methicillin-resistant *S. aureus*, *Bacillus subtilis*, and *Acinetobacter baumannii*. Furthermore, active molecules are non-toxic to mammalian cell line.




> Benign synthesis of pyrazole derivatives
> 29 Novel molecules
> MIC as low as 0.78 μM (*S. aureus, MRSA, B. subtilis*, and *A. baumannii*)
> Non-toxic to mammalian cells

Microbial resistance to antibiotics is an unsolved American and global concern.[1] Without urgent and coordinated action, we are moving toward an era in which normal infections or minor injuries may become fatal. Guidelines from the Centers for Disease Control and Prevention (CDC) recommend combatting antibiotic resistance[2] by promoting the development of new antibiotics and new diagnostic tests for drug-resistant bacteria. The ESKAPE (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species) bacteria cause two-thirds of nosocomial infections in the United States, and these bacteria are effectively escaping the existing antibiotics. The need for combating bacterial resistance to existing drugs is greater than ever.[3]

*A. baumannii*, a Gram-negative bacterium, is normally found in soil and water. It is responsible for different diseases in humans. *A. baumannii* in particular causes 80% of the diseases associated with the *Acinetobacter* genus. *Acinetobacter* infections threaten the lives of people with weakened immune systems, chronic lung disease, and diabetes. *Acinetobacter* infection outbreaks commonly happen in healthcare settings, particularly intensive care units, and this bacterium can live in tracheostomy sites or open wounds for several days without causing infection.[4] Since 2003, the beginning of the Iraq war, several US service members have been infected by *A. baumannii* which is a huge problem in veterans.[5-6] It is challenging for the medical community to find new antibiotics that can treat the infected people with multi-drug resistant (MDR) *A. baumannii* because almost all the approved antibiotics have failed. In late February 2017, the World Health Organization (WHO) has released a list of 12 drug resistant bacteria that pose the greatest threat to human health and for which new